Utah Medicaid Pharmacy & Therapeutics Committee
Drug Class Review: Older Anticonvulsants

Barbiturates, Anticonvulsants 28:12.04
Primidone (Mysoline®)

Hydantoins 28:12.12
Ethotoin (Peganone®)
Phenytoin (Dilantin-125®, Dilantin®, Dilantin® Infatabs®, Dilantin® Kapseals®, Phenytek® and generics)

Succinimides 28:12:20
Ethosuximide (Zarontin®, Zarontin® Syrup)
Methsuximide (Celontin® Kapseals®)

Anticonvulsants, Miscellaneous 28:12.92
Carbamazepine (Carbatrol®, Epitrol®, Tegretol®, Tegretol® XR)
Valproate Sodium, Valproic Acid, Divalproex Sodium (Depacon®, Depakene®, Depakote®, Depakote® ER, Depakote® Sprinkle, Stavzor®)

Anticonvulsants, Miscellaneous 28:12.92 and 54:40.12 Carbonic Anhydrase Inhibitor
Acetazolamide (Diamox®)

Barbiturates 28:24.04
Pentobarbital (Nembutal® Sodium Solution)
Phenobarbital (Luminal® Sodium and generic)

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Prepared by:
Vicki Frydrych BS, PharmD, Clinical Pharmacist
University of Utah College of Pharmacy

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Executive Summary

Introduction

Bromide was the first anticonvulsant used clinically in the 19th century followed by phenobarbital in the early 20th century. Further discovery led to the development of less sedating agents of which phenytoin was the earliest. This was followed by the ability to study of "brain waves" and ushered in the era of seizure threshold measurement determinations for antiepileptic activity. Anticonvulsant medications have been identified with various mechanism of action and pharmacologic class This report focuses on the earlier anticonvulsants, including the barbiturates, pentobarbital, phenobarbital, and primidone; the hydantoins ethotoin and phenytoin, the succinimides ethosuximide and methsuximide; and the miscellaneous anticonvulsant agents acetazolamide, carbamazepine, and valproic acid derivatives.

Each of the ten agents are available in oral tablet or capsule formulations. Five of the ten agents are available for administration as oral liquid formulations; carbamazepine and phenytoin as suspensions, ethosuximide and valproic acid as syrups, and phenobarbital as an elixir. Divalproex is available in a sprinkle formulation. Carbamazepine and phenytoin are available as chewable tablets and extended release tablets. Divalproex is additionally formulated as a delayed-release tablet. Acetazolamide and carbamazepine are available as extended-release capsules and valproic acid and divalproex as delayed-release capsules. Four agents are available for injection: acetazolamide, pentobarbital, phenytoin, and valproate sodium.

These medications are each FDA approved for use in at least one seizure disorder: epilepsy (unspecified) for acetazolamide and primidone; generalized, tonic-clonic seizures for phenytoin; status epilepticus for pentobarbital and phenytoin; complex-partial seizures for ethotoin, phenytoin, and valproic acid derivatives; absence seizures for ethosuximide and valproic acid derivatives; refractory absence seizures for methsuximide; grand mal seizures for ethotoin; partial, generalized and mixed epilepsies for carbamazepine; partial and generalized seizures for phenobarbital; and treatment and prophylaxis of seizures during and following neurosurgery for phenytoin. Additional indications for acetazolamide include the treatment of acute mountain sickness, edema, and as adjunct therapy in glaucoma. Additional indications for carbamazepine include bipolar I disorder with acute manic or mixed episodes and trigeminal neuralgia Additional indications for pentobarbital include adjunct therapy in anesthesia, short-term treatment of insomnia, and sedation. Additional indications for valproic acid and divalproex include bipolar I disorder with acute manic or mixed episodes as well as migraine prophylaxis. Finally, phenobarbital is additionally indicated for use in sedation.

Treatment of epilepsy depends on the type of epilepsy of epilepsy syndrome identified. Pharmacotherapy may reduce the likelihood of recurrent seizures, associated morbidity and mortality, improve quality of life and reduce the risk of sudden unexpected death in epilepsy (SUDEP).

According to Clinical Practice Guidelines, decision making concerning antiepileptic therapy should involve the patient, parent and caregivers; consider race, genetic variability, culture and specific needs; involve the development of a comprehensive care plan involving primary and

secondary practitioners and individualize treatment considering seizure type, syndrome, patient age, concomitant medications, comorbidity, patient lifestyle and preferences. Important safety issues in patients with epilepsy, include adverse events, bone health, psychological issues, pregnancy, idiosyncratic and hypersensitivity reactions. The newer antiepileptic medications have not been shown clinically superior to the older agent's newer agents are considered to have a safety advantage. A summary of some of the first-line treatment recommendations are summarized below (agents under review are bolded).

Absence Seizures: **ethosuximide, valproic acid**

Generalized-Onset, Monotherapy: **valproate**, **phenobarbital,** lamotrigine**, carbamazepine**, oxcarbazepine

Generalized-Onset, Adjunctive: **valproate,** lamotrigine, levetiracetam, topiramate

Generalized, Refractory, Monotherapy**:** topiramate, oxcarbazepine, **carbamazepine**, zonisamide

Infantile Spasms: Vigabatrin with tuberous sclerosis, adrenocorticotropic hormone (ACTH) without tuberous sclerosis

Lennox Gastaut syndrome: **valproate**

Myoclonic: **valproate,** levetiracetam, lamotrigine, topiramate

Partial-Onset, Monotherapy: lamotrigine, **carbamazepine**, levetiracetam, **phenytoin, valproate**

Partial-Onset, Adjunctive: **carbamazepine,** gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, **valproate**, clobazam

Partial-Onset, Refractory, Monotherapy: lamotrigine, topiramate, oxcarbazepine

Partial-Onset, Refractory, Adjunctive: gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, zonisamide

Status Epilepticus: midazolam, lorazepam, **phenobarbital,** fosphenytoin, **phenytoin**, levetiracetam, **phenobarbital**, propofol, **pentobarbital**, thiopental

Clinical Efficacy

Absence seizures; Four Cochrane reviews and other trials suggest that ethosuximide and valproic acid therapy yield similar rates of efficacy. Valproic acid is associated with lower tolerability including weight gain and attentional measures. A response to ethosuximide at 16-20 weeks is negative predictor for the long-term development of tonic-clonic seizures. Overall, ethosuximide provides similar efficacy with a superior safety profile than valproic acid.

Evidence finds no difference in efficacy between valproic acid and phenytoin for partial and generalized epilepsy. The time to first-post treatment seizure occurred more quickly with valproate for partial-onset seizures and phenytoin for generalized seizures. In children presenting with a second acute seizure in an emergency department valproic acid was superior to phenytoin only in the time to regain consciousness. These agents appear equally efficacious without clinical safety data.

Phenytoin and carbamazepine performed similarly across a variety of outcome measures in adults and children with generalized and partial onset seizures. No differences in safety were noted although carbamazepine therapy was associated with a higher discontinuation rate.

A Cochrane Review and small study found no difference between phenobarbital and phenytoin in the treatment of neonatal seizures, however, wide confidence intervals preclude considering the agents equivalent.

A meta-analysis found no difference in efficacy between carbamazepine and valproate in the treatment of partial onset and generalized epilepsy although confounding by epilepsy misdiagnosis could not be ruled out.

Methsuximide and acetazolamide afford benefit in the treatment of refractory epilepsy. Methsuximide reduced the seizure frequency in 33-50% of patients with refractory epilepsy that persisted 19 months to 3 years in 20-50% of patients. Acetazolamide demonstrated a beneficial response in the adjunctive treatment of refractory epilepsy in Japanese children most of whom had mental retardation. Approximately half of the patients (22/37) responded with a reduction in seizure frequency of at least 50% with 4 patients having a complete remission for more than 3 years. The combination of acetazolamide, carbamazepine and clonazepam performed statistically superior to other combinations. Although the response rates to methsuximide and acetazolamide are low and may not persist long term, these agents offer treatment option to patients with difficult to treat disease.

In the treatment of status epilepticus, lorazepam was more efficacious than valproate, phenytoin and phenobarbital but this may reflect the more rapid administration of lorazepam vs comparators. Valproate was found to be as effective as phenytoin and phenobarbital with better tolerability. Valproate also maintained a seizure free state for 24-hours post-dose better than phenobarbital and phenytoin.

In bipolar disorder, evidence supporting the role of valproic acid and divalproex was limited by high attrition, small numbers and short durations yielding conflicting outcomes and limiting generalizations. Adverse events rates were similar between treatment and placebo arms with divalproex associated with a higher frequency of constipation and back pain. A critical appraisal of valproate extended-release and delayed-release in studies limited by size, power, methodology and duration presented "practical practice information" that favored the extended-release product for its' potential to produce fewer concentration-related side effects and afford a once-daily dosing advantage. A mg-for-mg dosage conversion resulted in therapeutic concentrations in 95% of patients. Carbamazepine, was efficacious as monotherapy of bipolar disorder with manic, hypomanic or mixed symptomatology. Over 8 weeks, statistical improvement in measures of mania, depression, psychosis with 34% achieving remission. Treatment was associated with mild weight gain, statistically significant delay in cardiac conduction (PR and QRS interval prolongation) and reversible rash in 2 patients.

A Cochrane Review found valproic acid derivatives to be efficacious in the prophylaxis of migraine headache with ≥50% of patients reporting a reduction in headache frequency compared with placebo.

Safety

The available evidence is insufficient to identify any agent superior in safety to another.

Black Box Warnings: Carbamazepine, phenytoin and valproic acid derivative products include black box warnings. Carbamazepine carries a risk of fatal dermatologic reactions in patients of Asian descent with an inherited HLA-B*1502 allelic variant, may cause

agranulocytosis and agranulocytosis. Parenteral phenytoin administration at a rate >50 mg/min is associated with hypotension and cardiac arrhythmias and should be avoided. Failure of other therapies is the only valid indication for use of valproate in young children. Valproic acid derivative may cause potentially fatal hepatotoxicity in children below 2 years of age within the first 6 months of therapy. Risk factors include mitochondrial disease, mental retardation or organic brain disorder. Additionally, valproic acid use may cause life-threatening pancreatitis and is associated with impaired cognitive development and major congenital malformations (neural tube defects) limiting use in women of child-bearing age.

Contraindications: All the agents included in this review are contraindicated for hypersensitivity to the medication. Barbiturates, pentobarbital, phenobarbital and primidone are contraindicated in patients with a history of manifest or latent porphyria. Phenobarbital and pentobarbital are contraindicated in significant liver dysfunction or respiratory disease with dyspnea or obstruction. Of the hydantoin class of anticonvulsant medications, phenytoin is contraindicated in combination with delavirdine. Ethotoin is contraindicated for use in patients with hepatic abnormalities or hematologic disorders. Acetazolamide is contraindicated in people with sulfonamide sensitivity. It should not be used in hypokalemia, hyponatremia, with marked kidney, liver disease, dysfunction, hepatic encephalopathy, suprarenal gland failure or hyperchloremic acidosis. Long-term use should be avoided in patients with chronic, noncongestive angle-closure glaucoma. Carbamazepine use is contraindicated with nefazodone, monoamine oxidase inhibitors and in patients with a history of bone marrow depression. Valproic acid derivatives should not be used in people with urea cycle disorders or hepatic dysfunction.

Adverse Reactions: Neurological effects common with these medications, include sedation, fatigue, dizziness, coordination and cognitive impairment, mood, behavior changes and sexual dysfunction. Idiosyncratic, potentially life-threatening, cutaneous reactions occur with carbamazepine, phenytoin and the barbituates. Long-term adverse effects include gingival hyperplasia and hirsutism with phenytoin, shoulder-hand syndrome and Dupuytren's contractions with barbiturates, weight gain with valproate. The enzyme inducing antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and valproic acid) may produce lipid abnormalities and adversely affect bone status. Phenytoin may cause peripheral neuropathy, conduction delays and dystonias. Over the initial month of initiation of carbamazepine bone marrow dysfunction resulting in leukopenia, thrombocytopenia, agranulocytosis and rarely aplastic anemia may occur. Continued use may be associated with hyponatremia, conduction delays, anticholinergic effects that may impair absorption. Valproic acid use may result in thrombocytopenia, leukopenia, neutropenia, erythroblastopenia and pancreatitis. Elevated ammonia levels may occur both with and without concomitant hepatic failure.

Drug Interactions: The enzyme inducing antiepileptic agents, carbamazepine, phenytoin, phenobarbital and primidone can produce significant drug interactions by virtue of their activity to induce hepatic microsomal enzymes as well as by acting as substrates for these pathways. The need for multiple antiepileptic agents in at least 20% of patients with epilepsy and the increased frequency of epilepsy in the elderly who may receive a large number of chronic, maintenance medication increases the potential for adverse outcomes. These agents interact with other enzyme

inducing medications, interact with themselves by metabolic auto-induction and interact with other hepatically metabolized or eliminated medications. Women of child-bearing potential receiving an enzyme inducing antiepileptic medication require careful consideration of their birth-control regimen.

Summary:

The older antiepileptic medications remain the gold-standard for control of seizures in most epilepsy types and syndromes. Newer agents are not proven more efficacious. However, newer antiepileptic medications generally offer a better safety profile. Among the older antiepileptic medications, the enzyme inducing agents, carbamazepine, phenytoin, phenobarbital and primidone are associated with greater frequency and potential severity of adverse events than other agents.

In the treatment of epilepsy, ethosuximide provides similar efficacy with a superior safety profile than valproic acid including a reduction in long-term development of tonic-clonic seizures. In the treatment of generalized and partial-onset seizures no significant difference in efficacy was found in comparisons of phenytoin and valproic acid, phenytoin and carbamazepine, carbamazepine and valproic acid. In neonatal seizures, phenytoin and phenobarbital performed similarly. In the treatment of refractory epilepsy, acetazolamide and methsuximide demonstrated low, typically short-lived, clinically pertinent rates of efficacy. In status epilepticus, valproic acid may be preferred to phenytoin or phenobarbital as it demonstrated equivalent acute efficacy, higher tolerability and lower rates of recurring seizures over 24-hr.

Although labeled for use in bipolar disease, evidence is controversial for valproic acid. Use of valproate extended-release may be preferred to theoretically reduce adverse events and improve adherence over valproate delayed-release formulations in which a mg-for-mg conversion may yield therapeutic levels in 95% of patients. Carbamazepine use in bipolar disorder may be limited by adverse events including cardiac conduction delays and rash. Finally, Valproic acid derivatives appear efficacious in the prophylaxis of migraine headache.

Introduction

The history of seizures dates back to the Babylonians. Ancient peoples have considered seizures indicative of demonic possession; hence, the word "seizure" comes from the Latin, sacire "to take possession of". Greeks believed it to be a curse of the gods and referred to it as the Sacred Disease.[1,2]

Effective anticonvulsant pharmacotherapy began in the 19th century when bromide was found to reduce seizures.

The first medications used for seizures included bromide in the 19th century and phenobarbital as the first synthetic organic compound in the early 20th century.[3,4] It remained the treatment of choice until the development of phenobarbital in the early 20th century. Treatment was further advanced when phenytoin was found to have anticonvulsant activity without producing sedation.[4] Progress continued as the ability to study "brain waves" ushered in the era of seizure threshold measurements, allowing for the assessment of many chemical compounds potential antiepileptic activity. Development of primidone and ethosuximide was followed by the recognition of the anticonvulsant properties of the benzodiazepines, sodium valproate, carbamazepine followed by the development of the newer anticonvulsant medications. A wide variety of pharmacological classes were found to have anticonvulsant activity, including hydantoins (phenytoin, fosphenytoin, ethotoin), anti-seizure barbiturates (phenobarbital, pentobarbital), iminostilbenes (carbamazepine), succinimides (ethosuximide), valproic acid and derivatives, benzodiazepines (clonazepam, clorazepate, midazolam, diazepam, lorazepam, clobazam) and others (acetazolamide, brivaracetam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, magnesium sulfate, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin and zonisamide). The older anticonvulsant medications are very active antiepileptic medications, although wide use may be limited by adverse effects, drug interactions, safety concerns and risk:benefit ratios.[5]

Today's anticonvulsant armamentarium includes multiple pharmacologic classes which act by a variety of mechanisms of action. This report focuses on the safety and efficacy of the earlier anticonvulsants, including the barbiturates, pentobarbital, phenobarbital, and primidone; the hydantoins, ethotoin and phenytoin; the succinimides, ethosuximide and methsuximide; and the miscellaneous anticonvulsant agent's acetazolamide, carbamazepine and valproic acid derivatives.

Each of the 10 agents are available in oral tablet or capsule formulations.[6,7] Five of the 10 agents are available for administration as oral liquid formulations; carbamazepine and phenytoin as suspensions, ethosuximide and valproic acid as syrups and phenobarbital as an elixir. Valproic acid is available in a sprinkle formulation, delayed-release tablet, delayed-release capsule and extended-release tablet formulations. Carbamazepine and phenytoin are available as chewable tablets and extended-release tablets. Carbamazepine and acetazolamide are available as extended-release capsules. Four agents are available for injection; acetazolamide, pentobarbital, phenytoin and valproate sodium.

These medications are each FDA approved for use in at least one seizure disorder, including unspecified epilepsy (acetazolamide, primidone), generalized, tonic-clonic seizures

(phenytoin), status epilepticus (pentobarbital, phenytoin), complex-partial seizures (ethotoin, phenytoin, valproic acid/divalproex/valproate sodium), absence seizures (ethosuximide, valproic acid/divalproex/valproate sodium), refractory absence seizures (methsuximide), grand mal seizures (ethotoin), epilepsy, partial, generalized and mixed epilepsies (carbamazepine), partial and generalized seizures (phenobarbital), treatment and prophylaxis of seizures during and following neurosurgery (phenytoin). The following products have additional FDA-labeled indications. Acetazolamide is indicated for the treatment of acute mountain sickness, edema and as adjunct therapy in glaucoma. Carbamazepine is indicated in bipolar I disorder with acute manic or mixed episodes and trigeminal neuralgia. Pentobarbital is indicated as adjunct therapy in anesthesia, short-term treatment of insomnia and sedation. Phenobarbital is indicated for sedation. Valproic acid and divalproex are indicated in bipolar I disorder with acute manic or mixed episodes, migraine prophylaxis. **Table 1** compares the products and **Table 2** presents the Federal Drug Administration (FDA) labeled indications.

Table 1: Product Comparison

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Acetazolamide	**Generic** • Intravenous Powder for Solution: 500 mg • Oral Capsule, Extended Release: 500 mg • Oral Tablet: 125 mg, 250 mg **Acetazolamide (Novaplus)** • Intravenous Powder for Solution: 500 mg **Diamox Sequels** • Oral Capsule, Extended Release: 500 mg **PremierPro RX Acetazolamide** • Intravenous Powder for Solution: 500 mg	Acute mountain sickness: Treatment and prophylaxis Edema Epilepsy Glaucoma: Adjunct ***Unlabeled Use*** Prophylaxis for glaucoma following surgery Macular retinal edema Periodic ataxia	<u>Acute mountain sickness: Treatment and prophylaxis</u> • Initial: 24-48 hours before ascent: 500-1000 mg daily in divided doses or once daily with ER capsule. • Continue 48 hours or more at high altitude <u>Edema</u> • Congestive Heart Failure related ○ Initial: 250-375 mg (5 mg/kg) in the morning. Best with intermittent dosing (every other day or 2 days on and 1 day off) ○ Hold drug vs increase dose for nonresponse for kidney recovery • Acute Drug-Induced ○ 250-375 mg given for 1 or 2 days followed by a day off <u>Epilepsy</u> • 8-30 mg/kg in divided doses ○ 375-1000 mg daily • Adjunct: 250 mg once a day <u>Glaucoma: Adjunct</u> • Tablets: 250-1000mg in divided doses • Capsules (ER): 500 mg twice a day	Safety and efficacy is not established with capsule formulation in children <12 years of age or for tablets at any age Acute mountain sickness: Treatment and prophylaxis Age≥12 years: • Begin 24-48 hours before ascent • 500-1000 mg ER capsule in single or divided dosing • Rapid Ascent: 1000 mg daily • Continue 48 hours or more at high altitude Glaucoma: Adjunct • 8-30 mg/kg daily divided every 6-8 hours • 500 mg ER capsule twice daily	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Carbamazepine Carbamazepine	**Generic** • Oral Capsule, Extended Release: 100 mg, 200 mg, 300 mg • Oral Suspension: 100 mg/5 mL • Oral Tablet: 200 mg • Oral Tablet, Chewable: 100 mg • Oral Tablet, Extended Release: 100 mg, 200 mg, 400 mg **Carbatrol** • Oral Capsule, Extended Release: 100 mg, 200 mg, 300 mg **Epitol** • Oral Tablet: 200 mg **Equetro**	Bipolar I disorder, acute manic or mixed episodes Epilepsy: partial, generalized and mixed types Trigeminal neuralgia ***Unlabeled Use*** Agitation- dementia Alcohol withdrawal syndrome Behavioral syndrome	** Test patients for HLA-B*1502 allele with implicated ancestry <u>Bipolar I disorder, acute manic or mixed episodes</u> • Equetro®: Begin with 200 mg twice a day; increase by 200 mg daily to max studied dose of 1600 mg/day <u>Epilepsy: Partial, generalized and mixed types.</u> (Usual Dose 800-1200 mg/day, rarely 1600 mg/day) *Add gradually to anticonvulsant regimen: Doses remain constant or require a decrease with the exception of phenytoin where the dose may need to be increased.* • Suspension: Initial: 100 mg four times a day x 7 days; increase by 200 mg daily in divided doses every 7 days to usual dose Suspension produces higher peak levels than tablet/capsule. Start with low doses and increase slowly. • Tablet/Chewable Tablet: Initial: 200 mg twice a day x 7 days; increase by 200 mg daily in divided doses every 7 days to usual dose. • Extended-Release Tablet/Capsule: Initial: 200 mg twice daily x 7days; increase by 100 mg twice daily to usual dose <u>Trigeminal Neuralgia:</u> (Do not exceed 1200 mg/day) • Suspension: Initial: 50 mg four times a day, increase 50 mg four times a day to usual dose. Suspension produces higher	Equetro® safety and efficacy not established in pediatrics <u>Epilepsy: Partial, generalized and mixed types.</u> *Add gradually to anticonvulsant regimen: Doses remain constant or require a decrease with the exception of phenytoin where the dose may need to be increased.* **Suspension:** Suspension produces higher peak levels than tablet/capsule. Start with low doses and increase slowly. • Age <6 years: Initial: 10-20 mg/kg/day in divided doses; increase dose weekly to <35mg/kg/day • Age 6-12 years: 50 mg four times daily; increase weekly by 100 mg/day in 3-4 divided doses up to 800 mg/day MAX: 1000 mg/day • Age >12 years: Initial: 100 mg four times a day x 7 days; increase by 200 mg/day in 3-4 divided doses up to 1000 mg/day (age 12-15 years) or 1200 mg/day (age >15years) **Tablet or Chewable Tablet:** • Age <6 years: Initial: 10-20 mg/kg/day divided in 2-3 daily doses; increase weekly to <35 mg/kg/day • Age 6-12 years: Initial: 100 mg twice a day; increase weekly by 100	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	• Oral Capsule, Extended Release: 100 mg, 200 mg, 300 mg **Tegretol** • Oral Suspension: 100 mg/5 mL • Oral Tablet: 200 mg • Oral Tablet, Chewable: 100 mg **Tegretol-XR** • Oral Tablet, Extended Release: 100 mg, 200 mg, 400 mg		peak levels than tablet/capsule. Start with low doses and increase slowly. • Tablets, Chewable Tablets, Extended-Release Tablets: Initial: 100 mg twice a day; increase by 50 mg every 12 hours as needed for pain relief (200-1200 mg/day) • Extended-Release Capsule: Initial: 100 mg twice a day; increase by 100 mg every 12 hours • Maintenance: Every 3 months a trial dosage discontinuation or reduction to the minimum effective dosage. **Therapeutic Plasma Level: 4-12 mcg/mL**	mg in 3-4 divided doses up to 800 mg/day MAX: 100 mg/day • Age >12 years: Initial: 200 mg twice a day x 7 days; increase 200 mg in 3-4 divided doses up to 1000 mg/day (age 12-15) or 1200 mg/day (age >15) **Extended-Release Tablet or Capsule** • Age <6 years: • Age 6-12 years: **TABLET**: Initial: 100 mg twice a day; increase weekly by 50 mg twice a day up to 800 mg/day MAX: 1000 mg/day • Age <12 years: **CAPSULE:** Convert immediate-release product (≥400 mg/day) to same dose administered twice daily. • Age >12 years: **CAPSULE/TABLET**: Initial 200 mg twice a day x 7 days; increase 200 mg/day in 2 divided doses to 1000 mg (12-15 years) or 1200 mg/day (>15 years) **Therapeutic Plasma Level: 4-12 mcg/mL**	
Ethosuximide	**Generic** Oral Capsule, Liquid Filled: 250 mg Oral Syrup: 250 mg/5 mL	Absence seizures	<u>Absence Seizure:</u> • Initial: 500 mg once daily; increase every 4-7 days by 250 mg. • Higher doses may be administered in divided doses. • Doses of >1.5 gm/day require strict supervision.	<u>Absence Seizure:</u> <u>Age 3-6 years:</u> • Initial: 250 mg once daily; increase every 4-7 days by 250 mg. • Higher doses may be administered in divided doses.	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Zarontin Oral Capsule, Liquid Filled: 250 mg Oral Syrup: 250 mg/5 mL			• Doses of >1.5 gm/day require strict supervision <u>Age >6 years:</u> • Initial: 500 mg once daily; increase every 4-7 days to usual dose 20 mg/kg/day • Doses of >1.5 gm/day require strict supervision <u>Age 2.5-13 years:</u> • Initial: Titrate dosage upward by increasing dosage every 2 weeks. • Start with 10 mg/kg/day then 15 mg/day/day then 20 mg/kg/day then 30 mg/kg/day then 40 mg/kg/day then 50 mg/kg/day to target dosage which is the lower of 60 mg/kg/day or 2000 mg/day.	
Ethotoin	**Peganone** Oral Tablet: 250 mg	Complex partial epileptic seizure Grand mal seizure	*Maintain current doses of other epileptics while adding ethotoin and gradually decrease other agents as ethotoin dose is increased* <u>Complex Partial Epileptic Seizure:</u> • Initial: Increase gradually over several days to ≤1000 mg daily after food, in 4-6 evenly spaced, divided doses. • Maintenance: 2-3 gm/day after food, in 4-6 divided doses <u>Grand mal Seizure</u>: • Initial: Increase gradually over several days to ≤1000 mg daily after food, in 4-6 evenly spaced, divided doses. • Maintenance: 2-3 gm/day after food, in 4-6 divided doses	*Maintain current doses of other epileptics while adding ethotoin and gradually decrease other agents as ethotoin dose is increased* <u>Complex Partial Epileptic Seizure</u> Age ≥1 year: • Initial: Based on child age/weight uptitrate in 4-6 divided doses after food to MAX 750 mg/day • Maintenance: 500-1000 mg/day after food in 4-6 divided doses. • Doses up to 3 gm have been used	No

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
				<u>Grand mal Seizure</u> • Initial: Based on child age/weight uptitrate in 4-6 divided doses after food to MAX 750 mg/day • Maintenance: 500-1000 mg/day after food in 4-6 divided doses.	
Methsuximide	**Celontin Kapseals** Oral Capsule: 300 mg	Absence Seizure, Refractory	<u>Absence Seizure, Refractory</u> • Initial: 300 mg once a day x 7 days; increase by 300 mg/day weekly for 3 weeks to MAX 1.2 g/day in divided doses.	Absence Seizure, Refractory • Initial: 300 mg once a day x 7 days; increase by 300 mg/day weekly for 3 weeks to MAX 1.2 g/day in divided doses.	No
Pentobarbital	**Nembutal** Injection Solution: 50 mg/1 mL	Anesthesia: Adjunct Insomnia, short-term treatment Sedation Seizure: Emergency control of certain acute convulsive episodes (status epilepticus, cholera, eclampsia, meningitis, tetanus, toxic reactions to strychnine or local anesthetics) ***Unlabeled Use*** Raised intracranial pressures as a complication of traumatic injury	*Caution for withdrawal reaction* Individualize dose for age, weight and condition <u>Anesthesia: Adjunct</u> • 150-200 mg IM into a large muscle as a single injection. Repeat doses at 1 minute intervals to a total of 200-500 mg. <u>Insomnia, Short-term Treatment</u> • 150-200 mg IM into a large muscle as a single injection. Repeat doses at 1 minute intervals to a total of 200-500 mg. *Discontinue therapy by deleting a divided dose every 5-6 days* <u>Sedation</u> • 150-200 mg IM into a large muscle as a single injection. Repeat doses at 1 minute intervals to a total of 200-500 mg.	*Caution for withdrawal reaction* Individualize dose for age, weight and condition <u>Anesthesia</u> • Adjunct: 2-6 mg/kg IM into a large muscle as a single injection and up to a calculated proportionate reduction of a usual adult dosage (200-500 mg) <u>Insomnia, Short-term Treatment</u> • 2-6 mg/kg IM into a large muscle as a single injection and up to a calculated proportionate reduction of a usual adult dosage (200-500 mg) *Discontinue therapy by deleting a divided dose every 5-6 days*	No

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			Seizure, Emergency Control of Certain Acute Convulsive Episodes • 150-200 mg IM into a large muscle as a single injection. Repeat doses at 1 minute intervals to a total of 200-500 mg.	Sedation • 2-6 mg/kg IM into a large muscle, MAX 100mg/dose and up to a calculated proportionate reduction of a usual adult dosage (200-500 mg) Seizure, Emergency Control of Certain Acute Convulsive Episodes: • Use the minimum effective dosage to minimize seizure-associated CNS depression • 2-6 mg/kg IM into a large muscle as a single injection. • Followup Dosing: Proportionate reduction of a usual **adult dose (**100 mg IV at 50 mg/min supplemented with small doses at 1 minute intervals to MAX 200-500mg)	
Phenobarbital	**Generic** Oral Elixir: 20 mg/5 mL Oral Tablet: 15 mg, 16.2 mg, 30 mg, 32.4 mg, 60 mg, 64.8 mg, 97.2 mg, 100 mg **Generic** Injection Solution: 65 mg/1 mL, 130 mg/1 mL	Sedation Generalized and partial seizures ***Unlabeled Use*** Alcohol withdrawal Sedative/hypnotic withdrawal	Epilepsy • Tablet: 50-100 mg 2-3 times daily • Solution: 60-200 mg/day in divided doses Acute Convulsions • IM/IV: 20-320 mg, repeat every 6 hr as needed Sedation • Daytime sedation: 30-120 mg in 2-3 divided doses daily • MAX 400 mg/24 hours Preoperative Sedation • IM: 100-200 mg 60-90 minutes pre-op	Epilepsy • Tablet: 15-50 mg 2-3 times daily • Solution: 3-6 mg/kg/day in divided doses • IM/IV: 4-6 mg/kg/day for 7-10 days, use TDM Status epilepticus • IV: 15-20 mg/kg over 10-15 min. Sedation • Tablet: 6 mg/kg/day in 3 divided doses	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			Hypnotic • Tablet: 100-320 mg single dose • Solution: 100-200 mg • MAX 400 mg in 24 hours	Preoperative Sedation • IM/IV: 1-3 mg/kg	
Phenytoin	**Generic** • Oral Suspension: 125 mg/5 mL • Oral Tablet, Chewable: 50 mg **Dilantin-125** • Oral Suspension: 125 mg/5 mL **Dilantin Infatabs** • Oral Tablet, Chewable: 50 mg **Generic** • Oral Capsule, Extended Release: 100 mg, 200 mg, 300 mg **Dilantin Kapseals** • Oral Capsule, Extended Release: 30 mg, 100 mg **Dilantin**	Treatment or prophylaxis of seizure during neurosurgery Status epilepticus Generalized tonic-clonic, generalized and complex partial (psychomotor and temporal lobe) Seizures ***Unlabeled Indications*** Eclampsia and pre-eclampsia seizures Chronic pain Wound healing	*Free acid formulation contains 8% more phenytoin than sodium salt. Treatment or prophylaxis of seizure during neurosurgery Intravenous solution: • Administer 100-200 mg IM every 4 hours during surgery and throughout the postoperative period • Non-emergent: Loading Dose: 10-15 mg/kg administered not faster than 50 mg/min. Maintenance therapy with IV or oral administration every 6-8 hours • Use of IV formulation in patient receiving oral phenytoin: Continue the same daily dose, administered intravenously, not faster than 50 mg/min. NOTE: phenytoin plasma concentrations may increase. Oral tablets (Infatabs®) • 100 mg 3 times daily; increase to usual maintenance dose 300-400 mg/day; MAX 600 mg/day Extended-release capsule • Loading Dose in patients without renal or hepatic disease 1000 mg (400 mg, 300 mg, 300 mg) given at 2 hour intervals and begin maintenance therapy at 24 hours later	*Free acid formulation contains 8% more phenytoin than sodium salt. Treatment or prophylaxis of seizure during neurosurgery Intravenous solution: • Non-emergent: Loading Dose: 15-20 mg/kg IV administered not faster than 50 mg/min or 15-20 mg/kg (whichever is slower) • Use of IV formulation in patient receiving oral phenytoin: Continue the same daily dose, administered intravenously, not faster than 1-3 mg/kg/min or 50 mg/min (whichever is slower). NOTE: phenytoin plasma concentration may increase Oral tablets (Infatabs®) • Initial: 5 mg/kg/day in 2-3 divided doses; increase to usual maintenance dose 4-8 mg/kg/day; MAX 300 mg/day Extended-release capsules	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	• Oral Capsule, Extended Release: 30 mg, 100 mg **Phenytek** • Oral Capsule, Extended Release: 200 mg, 300 mg **Generic** • Injection Solution: 50 mg/1 mL **Phenytoin Sodium Novaplus** • Injection Solution: 50 mg/1 mL		• Initial: 100 mg 3 times daily; adjust dose every 7-10 days to usual maintenance dose of 300-600 mg/day in divided doses (patients maintained on 100 mg three times daily may be converted to 300 mg at bedtime) <u>Generalized tonic-clonic, generalized and complex partial (psychomotor and temporal lobe) seizures</u> Oral suspension • 125 mg three times daily; increase every 7-10 days to MAX 625 mg/day Oral tablets (Infatabs®) • 100 mg 3 times daily; increase to usual maintenance dose 300-400 mg/day; MAX 600 mg/day Extended-release capsule • Loading Dose in patients without renal or hepatic disease 1000 mg (400 mg, 300 mg, 300 mg) given at 2 hour intervals and begin maintenance therapy at 24 hours later • Initial: 100 mg 3 times daily; adjust dose every 7-10 days to usual maintenance dose of 300-600 mg/day in divided doses (patients maintained on 100 mg three times daily may be converted to 300 mg at bedtime) <u>Status epilepticus (intravenous solution)</u> • Loading Dose: 10-15 mg/kg IV not faster than 50 mg/min • Maintenance dose: 100 mg IV every 6-8 hours	• Initial: 5 mg/kg/day in 2-3 divided doses; increase every7-10 days to usual maintenance dose 4-8 mg/kg/day; MAX 300 mg/day <u>Seizure, Generalized Tonic-Clonic and Complex Partial (psychomotor and temporal lobe) Seizures</u> Oral Suspension/Tablets: • Initial: 5 mg/kg/day in 2-3 divided doses; increase to usual maintenance dose 4-8 mg/kg/day; MAX 300 mg/day Extended-release capsules • Initial: 5 mg/kg/day in 2-3 divided doses; increase every 7-10 days to usual maintenance dose 4-8 mg/kg/day; MAX 300 mg/day <u>Status epilepticus</u> • Loading Dose: 15-20 mg/kg IV not faster than 1-3 mg/kg/min or 50 mg/min (whichever is slower) • Neonates: 15-20 mg/kg IV no faster than 1-3 mg/kg/min	

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Primidone	**Generic** Oral Tablet: 50 mg, 250 mg **Mysoline** Oral Tablet: 50 mg, 250 mg	Epilepsy, adjunct or monotherapy ***Unlabeled Use*** Tremor	<u>Epilepsy, adjunct or monotherapy</u> • No previous treatment: Initially 100-125 mg at bedtime for 3 days, then twice daily for 3 days; then 3 times daily for 3 days, then 250 mg 3 times daily • Maintenance: 250 mg 3 or 4 times daily MAX: 2000 mg/day Receiving other anticonvulsants: • Initial 100-125 mg at bedtime. Increase primidone while other drug dose is decreased to appropriate combination or discontinuation of therapy with original agent over at least 2 weeks.	<u>Epilepsy, adjunct or monotherapy</u> Age ≥8 years <u>No previous treatment:</u> • Initially 100-125 mg at bedtime for 3 days, 100-125 mg twice daily for 3 days, 100-125 mg 3 times daily; then 250 mg 3 times daily • Maintenance: 250 mg 3-4 times a day; MAX: 2000 mg/day <u>Receiving other anticonvulsants:</u> • Initially 100-125 mg at bedtime. Increase primidone while other drug dose is decreased to appropriate combination or discontinuation of therapy with original agent over at least 2 weeks. Age <8 years: • Initially 50 mg at bedtime for 3 days, 50 mg twice daily for 3 days, 100 mg twice daily for 3 days, then 125-250 mg 3 times daily • Maintenance: 125-250 mg 3 times a day or 10-25 mg/kg/day in divided doses	Yes
Valproic Acid	**Generic** Oral Capsule, Liquid Filled: 250 mg	Absence seizure, simple and complex Complex partial epileptic seizure	*Divided dosing for doses > 250 mg* *Orphan Drug: Fragile X syndrome* *Dose to serum levels of 50-100 mcg/mL*	*Divided dosing for doses > 250 mg* *Orphan Drug: Fragile X syndrome* *Dose to serum levels of 50-100 mcg/mL* <u>Absence seizure, simple and complex</u>	Yes (some)

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Oral Syrup: 250 mg/5 mL **Depakene** Oral Capsule, Liquid Filled: 250 mg Oral Syrup: 250 mg/5 mL **Stavzor** Oral Capsule, Delayed Release: 125 mg, 250 mg, 500 mg	Manic bipolar I disorder Migraine, prophylaxis ***Unlabeled Use*** Myoclonic seizure	<u>Absence seizure, simple and complex</u> • Initially: 15 mg/kg/day • Maintenance: Increase 5-10 mg/kg/day at 1 week intervals to MAX 60 mg/kg/day <u>Complex partial epileptic seizure</u> Monotherapy: • Initially 10-15 mg/kg/day, increase 5-10 mg/kg/day at weekly intervals to MAX 60 mg/kg/day Conversion to monotherapy: • Initially 10-15 mg/kg/day, increase by 5-10 mg/kg/day at weekly intervals while decreasing concomitant drug by 25% every 2 weeks to MAX 60 mg/kg/day Adjunct to current regimen: • Initially 10-15 mg/kg/day; increase 5-10 mg/kg/day at weekly intervals to MAX 60 mg/kg/day <u>Manic bipolar I disorder</u> • Initially: 750 mg DR in divided doses to MAX 60 mg/kg/day <u>Migraine, prophylaxis</u> • Initially: 250 mg DR twice daily to MAX 1000 mg/day	Age 2.5-13 years: • Initially 10 mg/kg/day for 2 weeks; 15 mg/kg/day for 2 weeks; 20 mg/kg/day for 2 weeks; 30 mg/kg/day for 2 weeks; 40 mg/kg/day for 2 weeks; 50 mg/kg/day for 2 weeks to MAX 60 mg/kg/day or 3000 mg/day Age >10 years: • Initially 150 mg/kg/day; increase 5-10 mg/kg/day at weekly intervals to MAX 60 mg/kg/day <u>Complex partial epileptic seizure</u> Age ≥10 years Monotherapy: • Initially 10-15 mg/kg/day, increase 5-10 mg/kg/day at weekly intervals to MAX 60 mg/kg/day Conversion to monotherapy: • Initially 10-15 mg/kg/day, increase by 5-10 mg/kg/day at weekly intervals while decreasing concomitant drug by 25% every 2 weeks to MAX 60 mg/kg/day Adjunct to current regimen: • Initially 10-15 mg/kg/day; increase 5-10 mg/kg/day at	

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
				weekly intervals to MAX 60 mg/kg/day <u>Migraine, prophylaxis</u> Initially: 15-30 mg/kg/day in 2 divided doses.	
Divalproex	**Generic** Oral Capsule, Delayed Release: 125 mg Oral Tablet, Delayed Release: 125 mg, 250 mg, 500 mg Oral Tablet, Extended Release: 250 mg, 500 mg **Depakote ER** Oral Tablet, Extended Release: 250 mg, 500 mg **Depakote** Oral Tablet, Delayed Release: 125 mg, 250 mg, 500 mg **Depakote Sprinkles** Oral Capsule, Delayed Release: 125 mg	Absence seizure Complex partial epileptic seizure Manic bipolar I disorder Migraine prophylaxis ***Unlabeled Use*** Bipolar I disorder, maintenance Bipolar II disorder, maintenance Headache disorder, chronic	*Divided dosing for doses > 250 mg *Dose to serum levels of 50-100 mcg/mL *Convert from valproic acid via divalproex sprinkle capsule with same regimen; when stable convert to 2-3 divided doses daily *Convert delayed-release to ER by increasing daily ER dose 8-20% over daily DR dose <u>Absence seizure, simple and complex</u> • Initially: 15 mg/kg/day; increase by 5-10 mg/kg/day weekly to MAX 60 mg/kg/day <u>Complex partial epileptic seizure</u> Monotherapy: • Initially 10-15 mg/kg/day; increase 5-10 mg/kg/day weekly to MAX 60 mg/kg/day Adjunct: • Initially 10-15 mg/kg/day; increase 5-10 mg/kg/day weekly to MAX 60 mg/kg/day Conversion to monotherapy: • Initially 10-15 mg/kg/day; increase weekly by 5-10 mg/kg/day to MAX 60 mg/kg/day while reducing concomitant medication by 25% every 2 weeks <u>Manic bipolar I disorder</u>	*Divided dosing for doses > 250 mg for delayed-release and sprinkle formulations* *Dose to serum levels of 50-100 mcg/mL* *Convert from valproic acid via divalproex sprinkle capsule with same regimen; when stable convert to 2-3 divided doses daily* *Convert delayed-release to ER by increasing daily ER dose 8-20% over daily DR dose* <u>Absence seizure, simple and complex</u> Age ≥10 years: • Initially: 15 mg/kg/day; increase by 5-10 mg/kg/day weekly to MAX 60 mg/kg/day <u>Complex partial epileptic seizure</u> Age ≥10 years Monotherapy: • Initially 10-15 mg/kg/day increasing by 10-15 mg/kg/day at weekly intervals to MAX 60 mg/kg/day Adjunct: • Initially 10-15 mg/kg/day; increase by 5-10 mg/kg/day weekly to MAX 60 mg/kg/day	Yes (some)

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			• Depakote ER: Initially 25 mg/kg/day daily; increasing rapidly to MAX 60 mg/kg/day • Depakote DR: Initially 750 mg daily in divided doses; increasing rapidly to MAX 60 mg/kg/day <u>Migraine prophylaxis</u> • Depakote ER: Initially 500 mg daily for 1 week, then increase to 1000 mg daily • Depakote DR: Initially 250 mg twice daily for 1 week, then increase to MAX 1000 mg daily	Conversion to monotherapy: • Initially 10-15 mg/kg/day, increase weekly by 5-10 mg/kg/day to MAX 60 mg/kg/day while reducing concomitant medication by 25% every 2 weeks.	
Valproate Sodium	**Generic** Intravenous Solution: 100 mg/1 mL **Depacon** Intravenous Solution: 100 mg/1 mL **PremierPro RX Valproate Sodium** Intravenous Solution: 100 mg/1 mL **Valproate Sodium Novaplus** Intravenous Solution: 100 mg/1 mL	Absence seizure, simple and complex Complex partial epileptic seizure ***Unlabeled Use*** Status epilepticus West syndrome	*Orphan drug for Wolfram syndrome* *Dose to serum levels of 50-100 mcg/mL* *IV formulation is for use when oral administration is temporarily not possible* *IV dosage=PO dosage when administered every 6 hours or more frequently* <u>Absence seizure, simple and complex</u> • Initially: 15 mg/kg/day and increase weekly by 5-10 mg/kg/day to MAX 60 mg/kg/day <u>Complex partial epileptic seizure</u> Monotherapy: • 10-15 mg/kg/day; increase weekly by 10-15 mg/kg/day to MAX 60 mg/kg/day Conversion to monotherapy: • Initially 10-15 mg/kg/day; increase weekly by 5-10 mg/kg/day to MAX 60 mg/kg/day while reducing concomitant medication by 25% every 2 weeks Adjunct:	*Orphan drug for Wolfram syndrome* Not established for age <10 years* <u>Absence seizure, simple and complex</u> Age ≥10 years Monotherapy: • 10-15 mg/kg/day and increase weekly by 10-15 mg/kg/day to MAX 60 mg/kg/day Conversion to monotherapy: • Initially 10-15 mg/kg/day; increase weekly by 5-10 mg/kg/day to MAX 60 mg/kg/day while reducing concomitant medication by 25% every 2 weeks Adjunct: • Add to current regimen at 10-15 mg/kg/day; increase 5-	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			• Add to current regimen at 10-15 mg/kg/day; increase 5-10 mg/kg/day weekly to MAX 60 mg/kg/day <u>Status epilepticus</u> • Loading dose: 20-30 mg/kg (range 15-45 mg/kg) administered by IV infusion at 6 mg/kg/min • Maintenance dose: 1-3 mg/kg/hr	10 mg/kg/day weekly to MAX 60 mg/kg/day <u>Status epilepticus</u> Loading dose: • 20-30 mg/kg (range 15-45 mg/kg) administered by IV infusion at 6 mg/kg/min • Maintenance dose: 1-3 mg/kg/hr OR • Loading dose: 20 mg/kg in 20 mL NS over 5-10 minutes at MAX 5-6 mg/kg/min, then 1 mg/kg/hr	

Table 2: Anticonvulsant Labeled Indications

	Epilepsy	Absence Epilepsy	Partial, generalized, mixed epilepsy	Complex Partial Seizures	Generalized and Partial Seizures	Generalized Tonic-Clonic	Seizure: Emergency Control of Certain Acute Convulsive Episodes	Seizure prophylaxis and treatment during and following neurosurgery	Anesthesia: Adjunct	Trigeminal Neuralgia	Migraine Prophylaxis	Sedation	Insomnia	Bipolar I disorder, acute mixed or manic	Glaucoma Adjunct	Edema	Acute Mountain Sickness: Treatment and Prophylaxis
Acetazolamide	X														X	X	X
Carbamazepine			X							X				X			
Ethosuximide		X															
Ethotoin				X		X											
Methsuximide		X*															
Pentobarbital						X	X		X			X	X				
Phenobarbital					X							X					
Phenytoin				X		X		X									
Primidone	X																
Valproic Acid				X							X			X			
Divalproex		X		X							X			X			
Valproate Sodium		X		X													

Key: DR=delayed release; MAX=maximum daily dose; *=refractory;

Disease Overview

Epilepsy

The International League Against Epilepsy (ILAE) defines an epileptic seizure as, "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."[8] Epilepsy is a common, chronic disease. It is the fourth most common neurologic disease in the United States (US) following migraine, stroke and Alzheimer's disease. The average incidence of epilepsy in the US is 150,000 cases per year, with 1 in 26 persons developing epilepsy sometime during their life.[9] It is estimated that 5.1 million US persons are affected by epilepsy; 4.3 million adults and 750,000 children.[10] Epilepsy displays a bimodal age distribution. The incidence of epilepsy is highest in children less than 5 years of age with another peak in the elderly.[11] The annual incidence of epilepsy in people between the ages of 65-69 is 85.9 per 100,000 people. At ages greater than 80, the incidence increases to 135 per 100,000 people.[12] Compared with the general population, active epilepsy is associated with more physician visits (86.45 vs 66.1%).[14] Older patients with epilepsy visit a physician more often than younger adults with epilepsy (93.1% vs 65.7%). Epilepsy is associated with life expectancy reductions of as much as 10 years.[13,14] The standardized mortality rate (SMR) for epilepsy is 1.6-9.3 times higher than in the general population.[14] Mortality is 2-3 times higher in elderly patients with epilepsy than those without. Seizures in the elderly often present as status epilepticus, associated with a 40% mortality rate, and are a strong predictor for stroke. Conversely, stroke (cerebrovascular disease) acts as a risk factor for epilepsy, increasing risk of epilepsy by 20%. The strong interplay between epilepsy and stroke risk defines one basis for the higher incidence of epilepsy observed in the elderly. Reports of anticonvulsant use in the elderly find 10% of patients in nursing homes and 20% in a Veterans administration setting receive more than one anticonvulsant medication with 42-79% (respectively) receiving the medication for a non-epilepsy diagnosis.[12,15-18] Older veterans with an epilepsy diagnosis had lower physical and mental health status scores than those without ($p<0.01$), whether newly or previously diagnosed with epilepsy ($p\leq0.01$).[12,15-17]

Although 80% of patients with epilepsy are successfully treated with antiepileptic drugs, another 20-30% suffer with intractable, uncontrolled seizures, significant adverse events and higher morbidity and mortality.[19,20] Particular to epilepsy is the occurrence of sudden unexpected death in epilepsy (SUDEP) which may be responsible for up to 17% of deaths.[21] Epilepsy's greatest impact on quality of life relates to the effects of antiepileptic drug therapy on cognitive function and coordination.[22] The financial burden from informal care and medical expenditures associated with the treatment of epilepsy was $15.5 billion annually in the US.[23] The average lost lifetime wages associated with uncontrolled epilepsy is estimated at $317,000 for men and $140,000 for women.[24]

A seizure is a paroxysmal event resulting from abnormal neuronal activity in the cerebral cortex resulting in excessive excitation or loss of inhibition. [2,24] Simply stated, a seizure is the result of a malfunction in ion channels affecting neurotransmission through the synapse[2,24]. Seizures are single specific events which can recur. Seizures may result from hypoxia, ischemia, prenatal injury, developmental disorders (e.g. autism), head trauma, tumor, structural changes, stroke, Alzheimer's disease, infections, hypoglycemia, electrolyte abnormalities, medications or

genetic influences. Seizures occur from unidentifiable causes in up to two-thirds of people.[25] Differences in seizure presentation reflect the site of abnormal stimulation within the brain. The affected neocortex produces impulses which stimulate corresponding muscle fascicles producing seizure-like activity. A seizure may manifest with a loss of consciousness, an increase or decrease in muscle tone, paresthesias, Deja-vu, or hallucinations. Treatment of a seizure is directed toward reversing the etiology, when known. Epilepsy on the other hand, is a clinical disease process constituting a number of seizure types and etiologies which often requires chronic antiepileptic therapy.[2]

A standard definition of epilepsy was adopted by the ILAE in 2014.[26] ILAE updated and expanded the prior definition which was 2 or more unprovoked seizures occurring at least 24 hours apart to two or more unprovoked/reflex seizures occurring > 24 hours apart, or a single unprovoked/reflex seizure with and recurrence risk probability of at least 60% over the next 10 years following two unprovoked seizures or the diagnosis of an epilepsy syndrome.[26] ILAE defines epilepsy resolution as being past the age of an age-dependent epilepsy syndrome or off medications for 5 years with 10 seizure-free years. Using these definitions, ILAE defines the incidence of epilepsy between 0.3-0.5% and prevalence at 5 to 30 per 1000 persons.[2,26] Epilepsy is refractory or uncontrolled when even a single seizure occurs on therapy. Managing refractory epilepsy is important. Seizures may cause falls, broken bones, or SUDEP. Although two-thirds of patients will respond to medications, the remaining 1/3 of patients do not respond, continue to have seizures, and are at increased morbidity and mortality risk.[20] Epilepsy is not a single disease entity. It represents a range of underlying neurological disorders. Within the broad classification of epilepsy, an epilepsy syndrome involves a cluster of symptoms which may be specified by seizure type, age of onset, precipitating factor, specific part of the brain involved, EEG pattern, genetic predisposition, etc.[27]

Continuing advances in epidemiology, electrophysiology, neuroimaging, genomics and molecular biology have expanded our understanding of seizures and epilepsy. ILAE updated the classification system for seizures and epilepsy in 2010.[8] See Table 3 for the current ILAE classification system. New classifications combine clinical characteristic with specific electrophysiological findings.[28] Seizures are described by, 1) mode of onset as generalized (affecting both brain hemispheres), focal (originating and remaining limited to one brain hemisphere), and unknown (it remains unclear if these seizures are focalized, generalized or both; e.g. epileptic spasms). Epilepsy has a focal origin in approximately 2/3 of patients and generalized origin in 1/3 of patients, 2) etiology, now defined as genetic (e.g. Dravet syndrome), structural (e.g. congenital-tuberous sclerosis or acquired-trauma), metabolic (e.g. mitochondrial disorders), or unknown (normal imaging and no other etiology identified), 3) diagnostic specificity, determined with electro-clinical information (e.g. West syndrome), 4) distinctive constellations reflecting underlying pathology, some of which are known to respond to surgical intervention (e.g. Rasmussen encephalitis), 5) structural or metabolic epilepsies now described by the underlying cause, 6) finally, 30% of epilepsies fall into a heterogeneous group of epilepsies of unknown cause.[8,29]

Table 3: Classification of Seizures[8]

1. Generalized Seizures
    a. Tonic-clonic
    b. Absence
        i. Typical
        ii. Atypical
        iii. Absence with Special Features
            1. Myoclonic Absence
            2. Eyelid Myoclonia
    c. Myoclonic
        i. Myoclonic
        ii. Myoclonic Absence
        iii. Myoclonic Tone
    d. Clonic
    e. Tonic
    f. Atonic
2. Focal Seizures
3. Unknown
4. Epileptic Spasm

Patients having a single seizure may not require pharmacologic treatment.[2,27,28] Avoiding the likely precipitant(s) is often sufficient. When more than one seizure occurs or there is risk of recurrence (e.g. abnormal MRI, EEG or partial-onset seizure) pharmacotherapy is recommended. In this case, anticonvulsant medications are chosen on the basis of the diagnosis of epilepsy type or syndrome.[2,27,28]

Generalized tonic-clonic seizures produce a loss of consciousness with tonic muscle spasms followed by repetitive clonic movements. [2,3,9,28,30] Vocalizations from air passing over the larynx, tongue biting, cyanosis, and loss of sphincter tone are common. Upon completion of the seizure, consciousness is regained often accompanied by post-ictal lethargy and confusion. Seizures can begin in both hemispheres of the brain (primary) or in one hemisphere that spreads to the other hemisphere (secondary). Aura's reflect a partial-onset seizure having hemispheric spread. Tonic and clonic seizures do not always occur together.[2,3,9,28,30]

Absence seizures occur most commonly in children.[2,3,9,28,30]The may cease in adolescence although development of a second type of seizure is not uncommon. Seizures begin abruptly, are associated with a short loss of consciousness lasting a few seconds to a half minute and are not associated with a post-ictal state. Manifestations may include a blank stare and upward eye rotation. Atypical absence seizures have a milder onset and offset. They are often associated with

a loss of muscle tone leading to a gradual slump or myoclonic jerks. EEG testing is often required to differentiate this seizure type and allow for selection of the appropriate therapy.[2,3,9,28,30]

Focal seizures may present with motor or sensory symptoms.[2,3,28,30] If the seizure remains within one hemisphere symptoms are asymmetric. Focal seizures may progress to a larger area within the same hemisphere or progress to include both hemispheres (secondary generalization). Consciousness is maintained and additional symptoms reflect the area of the brain that is affected. Symptoms may reflect motor (e.g. twitch), sensory (e.g. altered taste, smell, visual or auditory hallucinations) or psychic experiences (e.g. déjà vu). If focal impulses spread, the patient may lose consciousness, experience automatisms (e.g. lip smacking, wandering, picking at clothes) and exhibit a brief postictal period.[2,3,28,30]

Myoclonic seizures result in the brief contraction of a muscle or muscle group followed by relaxation. [9,30] These often present with very brief bilateral, symmetrical muscle jerking or twitching lasting only a few seconds. Juvenile myoclonic epilepsy has on onset around puberty, affects the upper body, is most commonly experienced upon awakening and persists throughout life.[9,30]

Atonic seizures result in a loss of muscle tone. Manifestations may include eyelid drooping, head nodding, dropping of a limb or slumping to the ground.[9,30]

Epilepsy may present with a particular seizure type or in combination with other findings, including specific precipitating factors, EEG patterns, severity, chronicity, age of onset, family history or prognosis. [9,11,31-35] Some constellations of signs may constitute an epilepsy syndrome. West Syndrome (Infantile Spasms) is a rare age-specific epileptic disorder of infancy and early childhood (incidence of 0.015–0.02% in children ≦10 years of age) of which 90% of cases are diagnosed in the infant's first year.[9,11,31-35]

West Syndrome is associated with three main characteristics: infantile spasms, mental retardation, and hypsarrhythmia. Other common characteristics include psychomotor retardation and impaired mental development. Although 90% of children become seizure free by age 5, up to 50% will develop another seizure disorder.[9,11,14,31-33,36]

Lennox-Gastaut syndrome (LGS) is an age-specific epilepsy syndrome accounting for 1-10% of childhood epilepsies.[37,38] One-fifth of cases are preceded by West's syndrome. It most commonly affects males between 3-5 years of age although it has been diagnosed in children up to 8 years. LGS is characterized by a triad of signs including multiple types of epileptic seizures, abnormal slow spike waves on the wakening EEG and severe intellectual impairment. Behavioral and psychiatric comorbidities are common (i.e. Attention-deficit hyperactivity disorder, anxiety, aggressive behavior, psychosis and depression).[37,39] Juvenile myoclonic epilepsy (JME) is another epilepsy syndrome affecting children and adolescents age 6-22 years with 50% of cases found in 13-16 year olds. JME is characterized as a generalized epilepsy with myoclonic jerks upon awakening and specific EEG findings. Treatment of JME is challenging. Life-long pharmacotherapy is required and often associated with significant adverse events. Problematically, up to 20% of patient do not respond to therapy.[40,41]

The diagnosis of epilepsy or an epilepsy syndrome is crucial in determining treatment options. Clinicians may not witness the seizure. Astute observation and detailed reporting are important in diagnosing epilepsy. Factors that assist in making a diagnosis include what the person was doing prior to the seizure, the manifestation of symptoms including changes which may reflect generalization, time of day, duration or seizure, loss of consciousness, other movements, vocalizations, the patient's status following the seizure and the length of time before returning to baseline. Assessment continues with a medical history, neurologic examination and diagnostic testing (e.g. EEG, CT scan or MRI).[9]

Treatment of epilepsy depends on the type of epilepsy or epilepsy syndrome identified. Pharmacotherapy may reduce the likelihood of recurrence, reduce associated morbidity and mortality, increase quality of life and lessen the risk for SUDEP.[2] Achieving early control of seizures enhances the likelihood that long-term therapy may result in successful discontinuation of antiepileptic drug therapy in the future.[30] Non-pharmacologic treatments may include surgery, dietary modifications (ketogenic diet), vagus nerve stimulation and avoidance of any suspected precipitogen (e.g. alcohol, lack of sleep, caffeine, flashing/flickering lights). The goal of pharmacotherapy in epilepsy is to reduce, control, or eliminate seizures without causing unacceptable adverse side effects.[42]

A number of antiepileptic medications have been associated with the exacerbation or precipitation of seizures in treated patients. This may occur when the original diagnosis of the seizure type or syndrome was in error, when a seizure-specific-contraindicated-agent was administration and in the presence of high doses or polypharmacy. Further research is needed to elucidate the epileptogenic mechanisms.[43]

Decision making concerning antiepileptic therapy should involve the patient, parent and caregivers; give consideration to race, culture and specific needs; involve the development of a comprehensive care plan involving primary and secondary practitioners; and individualize treatment considering seizure type, syndrome, patient age, concomitant medications, comorbidity, patient lifestyle and preferences.[44,45] Important safety issues, include adverse events, bone health, psychological issues, pregnancy and SUDEP. Briefly, the most commonly recommended antiepileptic drugs for the various epilepsies/syndromes are found in **Table 4.** Clinical practice guidelines for the treatment of epilepsy are found in **Table 5.**

Table 4: Abbreviated Recommendations from Clinical Practice Guidelines

Epilepsy Type or Syndrome	Recommended Medications
Absence Seizures	Ethosuximide, valproic acid
Infantile Spasms	Tuberous sclerosis: Present- vigabatrin; Absent- adrenocorticotropic hormone (ACTH)
Lennox-Gastaut Syndrome	Valproate
Partial-Onset, Monotherapy	Lamotrigine, carbamazepine, levetiracetam, phenytoin, valproate
Partial-Onset, Adjunctive	Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate, clobazam
Generalized-Onset, Monotherapy	Valproate, phenobarbital (children), carbamazepine (children), lamotrigine, oxcarbazepine phenytoin
Generalized-Onset, Adjunctive	Valproate, lamotrigine, levetiracetam, topiramate
Partial-Onset, Refractory, Monotherapy	Lamotrigine, topiramate, oxcarbazepine
Partial-Onset, Refractory, Adjunctive	Gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, zonisamide
Generalized, Refractory, Monotherapy	Topiramate, oxcarbazepine, carbamazepine, zonisamide
Myoclonic	Valproate, levetiracetam, lamotrigine, topiramate
Status Epilepticus	Midazolam, lorazepam, phenobarbital, fosphenytoin, phenytoin, valproic acid, levetiracetam phenobarbital, propofol, pentobarbital, thiopental

Table 5: Clinical Practice Guidelines for the Treatment of Epilepsy

Guideline	Recommendations
Efficacy and tolerability of the new antiepileptic drugs, I: Treatment of new-onset epilepsy **Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society (2004)[19]**	Agents evaluated, included gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide Monotherapy in Newly Diagnosed Partial/Mixed Seizure disorder (adult and adolescent) • Recommend: Gabapentin, lamotrigine, topiramate and oxcarbazepine (level A) • Base selection on specific individual characteristics (level A) • Absence Seizures in Children • Recommend: Lamotrigine (level B)
Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy **Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society (2004) [19]**	Agents evaluated, included gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide as well as older established antiepileptic drugs Monotherapy in refractory partial epilepsy • Oxcarbazepine and topiramate (level A evidence) • Lamotrigine (level B evidence) • Insufficient evidence for gabapentin, levetiracetam, tiagabine or zonisamide Partial Epilepsy Add-on therapy in refractory partial therapy • Appropriate agents: gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam and zonisamide ○ Efficacy and side effects increase with increasing doses. Slow titration recommended ○ Oxcarbazepine had the highest drop-out rate at the highest dose (67%) Refractory Generalized Epilepsy • Topiramate is effective in adults and children

Guideline	Recommendations
	• Insufficient evidence for other agents • Children: Refractory Partial Epilepsy Adjunctive Therapy • Evidence supports gabapentin, lamotrigine, oxcarbazepine and topiramate Safety concerns • rash with lamotrigine • hypohidrosis with zonisamide and topiramate • Lennox-Gastaut Syndrome Evidence supports lamotrigine and valproic acid Appropriate agents for drop attacks: topiramate and lamotrigine Caution for worsening myoclonic seizures: lamotrigine and gabapentin
Summary of recommendations for the management of infantile seizures **Task Force Report for the ILAE Commission of Pediatrics(2015) [46]**	Infants with tuberous sclerosis complex • Vigabatrin (level C) ○ Non-response ACTH/oral steroids Infants without tuberous sclerosis complex • ACTH for short-term control of spasms (level B) • Alternative options: oral steroids, vigabatrin, valproate (level C) ○ ACTH/oral steroids may → better long-term neurodevelopmental outcome in children with epileptic spasms due to unknown etiologies than vigabatrin (level C evidence) • Continuing hypsarrythmia +/- spasms • Vigabatrin, valproate, benzodiazepines, topiramate, levetiracetam, surgery, ketogenic diet
Evidence-based guideline update: medical treatment of infantile spasms **Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)[47]**	Evidence Supports • Vigabatrin for short-term treatment of infantile spasms (excluding tuberous sclerosis complex) (Grade C) • ACTH remains preferred with Grade B evidence supporting both treatment response and improved neurodevelopmental outcomes. Insufficient Evidence • Evidence is insufficient to support treatment with valproic acid, levetiracetam, zonisamide or topiramate.
Evidence-based guideline: Management of an unprovoked first seizure in adults **Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (2015)[48]**	A first, unprovoked seizure has a recurrence rate of 21-45% over 2 years. • Recurrence rate increases with stroke, trauma, abnormal EEG, imaging abnormality or nocturnal seizures • Recurrence rate may be reduced by 35% over 2 years with use of antiepileptic drugs Antiepileptic drugs do not increase quality of life over 3-year period At 3 years, post-seizure, use of antiepileptic therapy affords no benefit in seizure remission or prognosis A second seizure increases the risk of additional seizures by 57% at 1 year, 73% at 4 years • Antiepileptic therapy is recommended after a second seizure

Guideline	Recommendations
ILAE treatment guidelines evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. **International League Against Epilepsy (2006)[49]**	Partial-Onset Seizures in Adults Newly Diagnosed or Untreated (Noted a paucity of Class I and Class II RCTs) • First-line mono-therapy may include phenytoin and carbamazepine (Grade A) or valproic acid with a rating of probably efficacious/effective (Grade B) • Evidence supports a rating of possibly efficacious/effective for gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin (Grade C) • Evidence supports a rating of potentially efficacious/effective for clonazepam and primodone (Grade D) Partial-Onset Seizures in Children Newly Diagnosed or Untreated (Noted a paucity of Class I and Class II RCTs) • First-line mono-therapy recommendation is oxcarbazine (Grade A) • Rated as possibly efficacious/effective are carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid (Grade C) • Rated as potentially efficacious/effective are lamotrigine and vigabatrin (Grade D) Partial-Onset Seizures in Elderly Adults (Noted a paucity of Class I and Class II RCTs) • First-line monotherapy may include lamotrigine or gabapentin (Grade A) • Rated as possibly efficacious/effective for initial monotherapy is carbamazepine (Grade C) • Rated as potentially efficacious/effective for initial monotherapy are topiramate and valproic acid (Grade D) Generalized-Onset Seizures in Adults (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly effective/efficacious with carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin topiramate and valproic acid (Grade C) • Drugs which should be used with caution because they may aggravate or precipitate generalized tonic-clonic or other generalized seizures include oxcarbazepine and phenytoin (Grade D) • Rated as potentially efficacious/effective as initial monotherapy are gabapentin and vigabatrin (Grade D) Generalized-Onset Seizures in Children (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly efficacious/effective with carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid (Grade C) • Rated as potentially efficacious/effective as initial monotherapy is oxcarbazepine. • Drugs which should be used with caution because they may aggravate or precipitate generalized tonic-clonic or other generalized seizures include carbamazepine, oxcarbazepine and phenytoin (Grade D) Absence Seizures in Children (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly efficacious/effective with ethosuximide, lamotrigine or valproic acid (Grade C) • Rated as inefficacious/ineffective is gabapentin (Grade F) • The following AEDs may precipitate absence seizures, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin (Grade D)

Guideline	Recommendations
	Children with benign epilepsy with centrotemporal spites (BECTS) (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly efficacious/effective with carbamazepine and valproic acid (Grade C) • Rated as potentially efficacious/effective are gabapentin and sulthiame (Grade D) • Some data supports anticonvulsive therapy may not be necessary (Grade D) Juvenile Myoclonic Epilepsy (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A, B or C) • First-line monotherapy recommendations which may have some efficacy, include carbamazepine, lamotrigine, levetiracetam, topiramate, valproic acid or zonisamide (Grade D) • The following AEDs may precipitate or aggravate absence and myoclonic seizures, carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and valproic acid
Diagnosis and management of epilepsy in adults. **Scottish Intercollegiate Guidelines Network [SIGN 143] (2015)[50]**	Focal Onset Seizures Monotherapy • Lamotrigine is the drug of choice ○ Carbamazepine and levetiracetam are options when lamotrigine is not tolerated (Grade A) Focal Onset Epilepsy Adjunct Therapy • Carbamazepine, gabapentin, Lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproate and zonisamide (Grade A) Generalize Epilepsy Adjunct Therapy • Lamotrigine, levetiracetam ethosuximide, valproate and topiramate (Grade A) • Match drug choice to the type of seizure and limit to 2-3 antiepileptic medications (Grade B) Genetic Generalized Epilepsy or Unclassified Epilepsy • Valproate is the drug of choice. ○ Lamotrigine and topiramate are options when valproate is not tolerated and in women of childbearing age (Grade A) ○ Recommend against switching between manufacturers Management of Older Adults with Epilepsy • Focal-onset seizures: Consider lamotrigine or levetiracetam first-line (Grade B) • Gabapentin is an alternate for monotherapy or adjunct therapy Drug-resistant Epilepsy • Failure to respond may reflect an incorrect diagnosis or adherence issues • Use combination therapy after treatment with two first-line agents have failed or only a reduction of seizures during phased substitution Provoked Seizures • Long-term prophylaxis is not indicated, treatment for provoked seizures should be discontinued and drug therapy is not indicated for concussive convulsions Adverse Drug Effects • Patients should be educated about common adverse effects, instructed to seek medical care urgently if rash, bruising, somnolence or vomiting occur particularly during the first week(s) of treatment. • Routinely monitor liver function and complete blood count

Guideline	Recommendations
	Bone Health • To reduce the risk of osteoporosis, patients should receive dietary and lifestyle advice Psychiatric/Behavioral Adverse Effects • The choice of antiepileptic agent should include consideration of these negative psychotropic effects (Grade B) Pregnancy • Discuss contraception, pre-pregnancy counseling (Grade B) • Discuss fetal, neonatal/childhood outcomes, breastfeeding
Epilepsies: Diagnosis and Management **National Institute for health and Care Excellence (NICE) [CG137] (2012)[51]**	General Considerations • Recommendations included for children (28 days to 11 years), adolescents/young people (12-17 years), adults (> 18 years) and older people (> 65 years) • Antiepileptic drug treatment (AED) should be individualized with consideration for type of seizure, epilepsy syndrome, co-medication and co-morbidity, patient's lifestyle and preferences of patient, family and/or caregivers. Sudden unexpected death in epilepsy (SUDEP) ○ Discuss the importance of optimizing seizure control and the consequences of nocturnal seizures • Diagnosis: Every attempt should be made to determine the diagnosis/etiology • Monotherapy is preferred when possible. At least two monotherapy trials of alternative agents should be attempted • Add new agent to old, titrate to 'therapeutic' dose and taper off first drug • Women & Girls ○ Discuss therapy with females of childbearing potential and younger girls likely to require treatment as they become of child-bearing potential and their caregivers and parents ○ Counsel regarding contraception, conception, pregnancy, caring for children, breast-feeding and menopause ○ Risk of AED-caused malformations, possible neurodevelopmental impairments with different agents, especially valproate with increased risk at doses > 800 mg/day and polytherapy. ○ Progesterogen: Progesterogen-only pills and implants are not recommended ○ Use of enzyme-inducing antiepileptic drugs and oral contraception or depot progesterogen should consider additional barrier method contraception. ○ Estrogen-based contraceptive use may reduce lamotrigine serum levels and loss of seizure control ○ Offer folic acid 5 mg/day for women/girls on antiepileptic drugs before they become pregnant • Monitoring AED levels routinely is not required; it may be helpful in pregnancy or when a loss of seizure control occurs, especially with phenytoin or lamotrigine • Older People: Careful consideration for pharmacokinetic/ pharmacodynamics issues, polypharmacy and comorbidities Focal Seizures (children, young people, adults) • First-line (newly diagnosed): Lamotrigine or carbamazepine

Guideline	Recommendations
	• If above are unsuitable/not tolerated/ineffective: levetiracetam, oxcarbazepine, valproate. Refractory Focal Seizures Adjunctive Treatment (children, young people, adults) • Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate • Tertiary care providers may consider eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide. • Risk: benefit vigabatrin due to potentially irreversible effects on visual field. Generalized Tonic-Clonic Seizures (GTC) (children, young people, adults) • First Line (newly diagnosed): valproate • If valproate is unsuitable consider lamotrigine • Lamotrigine may exacerbate myoclonic seizures or juvenile myoclonic epilepsy • Consider: carbamazepine and oxcarbazepine • Caution: may exacerbate myoclonic and absence seizures Generalized Tonic-Clonic Seizures, Adjunctive Treatment (children, young people, adults) • First Line: Clobazam, lamotrigine, levetiracetam, valproate or topiramate • Myoclonic/absence seizure risk, avoid carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin Absence Seizures (children, young people, adults) • First Line: Ethosuximide, valproate (valproate preferred with a history of GTC seizures) • Alternative: Lamotrigine Absence Seizures, Adjunctive Treatment (children young people, adults) • If two first-line agents fail, consider combination with two of ethosuximide, lamotrigine, valproate • If adjunctive therapy fails involve a tertiary epilepsy specialist who may consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide. DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Myoclonic Seizures (children, young people, adults) • First Line: Valproate • If valproate is unsuitable/not tolerated: Levetiracetam or topiramate Myoclonic Seizures Adjunctive Treatment (children, young people, adults) • Levetiracetam, valproate, topiramate • If adjunctive therapy fails involve a tertiary epilepsy specialist who may consider clobazam, clonazepam, piracetam or zonisamide. DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Tonic or Atonic Seizures (children, young people, adults) • First-Line: Valproate Tonic or Atonic Seizures (children, young people, adults) • First-Line: Valproate Tonic or Atonic Seizures Adjunctive Treatment (children, young people, adults) • Lamotrigine

Guideline	Recommendations
	• If adjunctive therapy fails involve a tertiary epilepsy specialist who may consider rufinamide or topiramate. DO NOT use carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. Infantile Spasms • Involve a tertiary epilepsy specialist • First Line (non-tuberous sclerosis): Prednisolone or tetracosatide or vigabatrin • First Line (tuberous sclerosis): Vigabatrin ○ If vigabatrin fails, use prednisolone or tetracosatide Dravet Syndrome (children) • Involve a tertiary epilepsy specialist: • Consider valproate, topiramate Dravet Syndrome (children, young people, adults) • Involve a tertiary epilepsy specialist: Clobazam or stiripentol • DO NOT use carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Lennox-Gastaut Syndrome (child) • Involve a tertiary epilepsy specialist • First Line: Valproate Lennox-Gastaut Syndrome Adjunctive Treatment (children, young people, adults) • Lamotrigine • DO NOT use carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin • Tertiary epilepsy specialist may consider rufinamide and topiramate ○ Felbamate is an option ONLY with epilepsy specialist care and all other treatments have proven ineffective or not tolerated. Benign Epilepsy with Centrotemporal Spikes (BECTS), Panayiotopoulos syndrome or Late-Onset Childhood Occipital Epilepsy (Gastaut type) (children, young people) • Determine with family, patient, caregivers if treatment is indicated • First-Line: Carbamazepine or Lamotrigine ○ If above are unsuitable/not tolerated/ineffective: levetiracetam, oxcarbazepine, valproate. Benign Epilepsy with Centrotemporal Spikes (BECTS), Panayiotopoulos syndrome or Late-Onset Childhood Occipital Epilepsy (Gastaut type) Adjunctive Treatment (children, young people) • Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate ○ If above are ineffective or not-tolerated, involve a tertiary epilepsy specialist who may consider: eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. ○ Risk: benefit vigabatrin due to potentially irreversible effects on visual field. Idiopathic Generalized Epilepsy (IGE) (children, young people, adults) • First-Line: Valproate ○ If above ineffective, unsuitable, not tolerated consider lamotrigine or topiramate ○ Lamotrigine may exacerbate myoclonic seizures

Guideline	Recommendations

	Idiopathic Generalized Epilepsy (IGE) Adjunctive Treatment (children, young people, adults)
	• Consider lamotrigine, levetiracetam, valproate or topiramate
	  ○ If above are ineffective or not tolerated, involve a tertiary epilepsy specialist who may consider: clobazam, clonazepam or zonisamide
	• DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin
	Juvenile Myoclonic Epilepsy (children, young people, adults)
	• First-Line: Valproate
	  ○ If above is unsuitable or not tolerated consider: lamotrigine, levetiracetam or topiramate
	  ○ Lamotrigine may exacerbate myoclonic seizures
	Juvenile Myoclonic Epilepsy Adjunct Treatment (children, young people, adults)
	• Consider: lamotrigine, levetiracetam, valproate or topiramate
	  ○ If above are ineffective or not tolerated involve a tertiary epilepsy specialist who may consider: clobazam, clonazepam or zonisamide
	• DO NOT offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin
	Generalized Tonic-Clonic Seizures (children, young people, adults)
	• First-Line: Lamotrigine, valproate (valproate is preferred with myoclonic seizures of juvenile myoclonic epilepsy)
	• Alternative first-line, may consider: carbamazepine, oxcarbazepine
	• Caution: May exacerbate myoclonic or absence seizures
	Generalized Tonic-Clonic Seizures Adjunctive Treatment (children, young people, adults)
	• First-Line: Clobazam, lamotrigine, levetiracetam, valproate, topiramate
	Childhood Absence Epilepsy, Juvenile Absence Epilepsy or other Absence Epilepsy Syndromes (children, young people, adults)
	• Ethosuximide, valproate (preferred with risk of generalized tonic-clonic seizures)
	  ○ If above are ineffective, unsuitable or not tolerated consider: lamotrigine
	Childhood Absence Epilepsy, Juvenile Absence Epilepsy or other Absence Epilepsy Syndromes Adjunctive Treatment (children, young people, adults)
	• If two of the above agents are ineffective, consider a combination of two agents (lamotrigine, valproate, ethosuximide)
	  ○ If above are ineffective or not-tolerated, involve a tertiary epilepsy specialist who may consider: clobazam, clonazepam, levetiracetam, topiramate or zonisamide
	• DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin
	Prolonged/Repeated Seizures and Convulsive Status Epilepticus (children, young people, adults)
	Community Setting:
	• First-line: Buccal midazolam
	• Rectal diazepam may be used if preferred or buccal midazolam unavailable
	• If intravenous is/becomes available, lorazepam (IV) may be used
	Hospital Setting:

Guideline	Recommendations
	• IV lorazepam (diazepam if lorazepam is unavailable or buccal midazolam if IV access is unavailable • Continued seizures: phenobarbital, phenytoin • Refractory Status Epilepticus (see published protocols) Other Syndromes, epilepsies, EEG abnormalities: Refer to tertiary epilepsy specialist Other Considerations: • Vigilance for treatment-emergent adverse effects • Assess and optimize adherence • Monitoring antiepileptic drug levels • Adherence issues • Suspected toxicity • Phenytoin dose adjustment • Management of pharmacokinetic interactions • Clinical conditions (e.g. pregnancy, organ failure, status epilepticus) • Treatment Discontinuation: When seizure free for at least 2 years, consider tapering-off one drug at a time over 2-3 months. Monitor for withdrawal symptoms and seizure recurrence. • Other Treatment Options ○ Psychological interventions (relaxation, cognitive behavioral therapy, biofeedback) ○ ketogenic diet ○ vagus nerve stimulation
Antiepileptic drug selection for people with HIV/AIDS **International League Against Epilepsy and American Academy of Neurology (2012)[52]**	Statistics • Seizures will develop in 2.6-6.1% of HIV patients • 55% of people taking antiretroviral medications may require an antiepileptic medication (AED) Pharmacotherapy • Phenytoin → increase dosage of lopinavir/ritonavir 50% • Valproic Acid → zidovudine dosage reduction may be required • Dosage adjustments are not required with combinations of valproic acid/efavirenz, lamotrigine/raltegravir/atazanavir • Lamotrigine → increase dosage increases of ritonavir/atazanavir 50% The use of enzyme inducing AEDs should be avoided when HIV/AIDS regimens include protease inhibitors or nonnucleoside reverse transcriptase inhibitors. If required, pharmacokinetic assessments are recommended to prevent antiviral treatment failure or the development of viral resistance.
Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) agrees to strengthen warnings on the use of valproate medicines in women and girls	Statement Concerning Use of Valproate Restrictions to valproate use due to • Birth defects when used in pregnant women, 11% ↑ • Developmental problems found in 30-40% of exposed children • Autism spectrum disorder 3x ↑ in exposed children Recommend provision of additional education and materials

Guideline	Recommendations
CMDh Medicines and Healthcare Products Regulatory Agency (MHRA):Pharmacovigilance and risk assessment committee (PRAC) (2014)[53]	Restrict routine valproate prescribing • Not used routinely for epilepsy or bipolar disorder in girls/women who are/might become pregnant. • Use only after other treatments fail or produce serious adverse effects. Valproate-treated women should use effective women
Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology **Arzimanoglou et al (2009)[37]**	Cochrane Review • Useful add-on therapies: lamotrigine, topiramate and felbamate • Drop attacks were reduced by lamotrigine and topiramate ○ Atonic seizures were reduced by felbamate • Tonic-clonic seizures were reduced by felbamate and lamotrigine (unreported for topiramate)
Treatment of Lennox-Gastaut Syndrome (LGS). **European Paediatric Neurology Society (2009)[38]**	Lennox-Gastaut Syndrome • First-line therapy is valproate • Second-line therapy is one or two of the following, lamotrigine, levetiracetam, rufinamide, topiramate, zonisamide • Third-line therapy following non-pharmacologic interventions (ketogenic diet, vagus nerve stimulation) and alternative second-line agents, consider acetazolamide, bromides, carbamazepine, ethosuximide, felbamate, phenobarbital, phenytoin, vigabatrin
EFNS Guideline on the Management of Status Epilepticus in Adults **Meierkord et al[54]**	<u>New onset generalized status epilepticus</u> • Intravenous lorazepam 4-8 mg (0.1 mg/kg) or diazepam 10 mg ○ Infusion time for lorazepam is shorter than diazepam • Follow immediately with phenytoin 18 mg/kg via rapid loading • Seizures continuing > 10 min after benzodiazepine dose ○ administer a second dose of lorazepam 4 mg or diazepam 10 mg <u>Refractory generalized status epilepticus</u> • Anesthetic doses of ○ Barbiturates ○ Propofol ○ Midazolam • Barbiturates and propofol dosing is titrated by EEG burst suppression for 24 hours <u>Non-convulsive status epilepticus</u> • Treatment varies by type and cause <u>Complex partial status epilepticus</u> • Treat as generalized status epilepticus • Refractory cases are not treated with anesthetics but rather levetiracetam, phenobarbital or valproic acid

Guideline	Recommendations
Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Results of the Guideline Committee of the American Epilepsy Society **Glauser et al[55]**	First-line Therapy • Benzodiazepine (Equivalent Options) ○ Midazolam IM (10 mg if >40kg, 5 mg for 13-40 kg) ○ Lorazepam IV (0.1 mg/kg/dose; MAX 4mg dose; May repeat x1 ○ Diazepam IV (0.15-2 mg/kg/dose; MAX 10 mg dose; May repeat x 1 • If unavailable, consider ○ Phenobarbital IV (15 mg/kg/dose) x 1 ○ Diazepam rectal (0.2-0.5 mg/kg; MAX 20 mg dose ○ Midazolam intranasal or buccal midazolam Persistent Status Epilepticus (Equivalent Options) ○ Fosphenytoin IV (20mg PE/kg; MAX 1500 mg dose) x 1 ○ Valproic Acid IV (40 mg/kg; MAX 3000 mg dose) x 1 ○ Levetiracetam (60 mg/kg; MAX 4500 mg dose) x 1 • If unavailable, and not already given, consider ○ Phenobarbital IV (15 mg/kg, MAX) If Seizures Continue (third-phase therapy) • Repeat second line therapy • Anesthetic doses of thiopental, midazolam, pentobarbital or propofol with continuous EEG monitoring

Key: EKG=electrocardiogram; AED=antiepileptic drug; EEG=electroencephalogram

Bipolar Disorder

Bipolar disorder (or manic-depressive disorder) is a mood disorder characterized by episodes of depression and mania.[56] The prevalence of bipolar disorder is 0.4 to 1.4% across the world and 4% in the US.[57,58] In general, bipolar disorder occurs more frequently in women than men and the average age of first onset of the disease is 25 years. Bipolar disorder is the most expensive mental health disorder, costs per affected individual doubling those of depression. The economic burden of bipolar disorder in the US results from indirect costs due to lost productivity resulting from absenteeism and presentism in addition to direct healthcare costs.[57] Bipolar disorder is also associated with an increased rate of substance abuse, legal and financial complications, relationship difficulties, self-harm and serious suicide attempts. Successful disease management and early treatment intervention can help to improve health outcomes and reduce the economic burden of bipolar disorders.[57]

The depression-mania cycles associated with bipolar disorder are unpredictable. Manic episodes typically emerge over a period of days to weeks and persist up to several weeks or months. Mania is defined as a clearly elevated mood with unrestrained behaviors lasting at least a week with at least 3 symptoms which may include irritability, grandiosity, sleeplessness, pressure talking, distractibility or engaging in activities with a high potential for adverse consequences. Clinical evidence suggests anger and agitation are the most common symptoms in pediatric patients while disordered thought content occurs most frequently in adult patients.[59] In severe mania, symptoms similar to those seen in schizophrenia, including delusions and paranoid thinking, may present. The depressive episodes are defined as a persistent low mood including lack of positive affect and anhedonia causing impairment for greater than 2 weeks. In bipolar II disorder patients may lack the full criteria for mania and the recurrent depression episodes are instead separated by hypomania episodes with mild activation and increased energy.[56,60]

Treatment of bipolar disorder includes psychotherapy and medication therapy (mood stabilizers and antidepressant medications).[61,62] Mood stabilizers may include lithium, anticonvulsant therapies and antipsychotic agents. Lithium is typically the first-line agent and has demonstrated efficacy in the treatment of bipolar disorder with a response rate of 70-80%, beneficial effects within 1-2 weeks and prophylactic effects. [62-65] Antidepressants are effective in treating breakthrough depression episodes but may precipitate mania or accelerate cycle frequency. Recent clinical evidence suggests mood stabilizers demonstrating efficacy for mania are also efficacious for mixed episodes, reducing the need for antidepressant therapy.[66] Antipsychotic agents (such as aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) may be used alone or in combination with other mood stabilizers or antidepressants to maintain mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy.[66,67]

Clinical guidelines for the treatment of bipolar disorder include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorder (2013)[68], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)[69] the National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014),[70] American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007),[71] the VA/DoD Clinical Practice Parameter For Management Of Bipolar Disorder In Adults (2010) and the Texas Medication Algorithm Project (TMAP) for the Treatment of Bipolar Disorder (2005). See **Table 6** for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment for acute manic and acute depressive episodes and maintenance therapy in patients at high risk for recurrence or severe disease. For selection of pharmacotherapy in the treatment of acute mania or depression episodes, factors to consider include: symptoms (such as euphoric, mixed, psychotic, suicidality), severity, treatment history, adverse effect profile and patient preference.[68,71-73]

Medication therapy for acute mania episodes (lithium, valproate, aripiprazole, risperidone, ziprasidone, etc.) should be continued until full remission.[71,74,75] If no response or only a partial response is achieved after 2 weeks of therapy, increase the dose of the medication or switch to another agent. Combination therapy is recommended in patients with continued treatment-resistance to a single agent. In patients with severe mania, clozapine or electroconvulsive therapy (ECT) may be indicated. Recommendations for antidepressant therapy in the treatment of acute depression episodes are inconsistent. In general, medication therapy for acute depressive episodes (antidepressants, lithium, quetiapine, olanzapine, lamotrigine, etc.) should be provided in an established treatment setting, in combination with behavioral therapy and regularly assessed for both efficacy and adverse effects. Before initiation of treatment for acute depression, all other potential medical causes should be ruled out and caffeine, alcohol and other substances should be discontinued. Of note, the full therapeutic effects of antidepressant therapy, lithium and lamotrigine may be delayed several weeks; short-term symptomatic treatment with benzodiazepines during the first few weeks of an acute bipolar episode may be required. Maintenance therapy is recommended in patients with three or more acute episodes, two acute episodes and a positive family history for bipolar disorder or in patients with severe disease.[62,65,68,71,72,74,76,77]

Table 6. Current Clinical Practice Guidelines for the Treatment of Bipolar Disorder

Guidelines	Recommendation
World Federation of Societies of Biological Psychiatry (WFSBP) (2013)[68]	Treatment of an acute mania episode, any one of the following: • Aripiprazole 15-30 mg daily • Lithium 600-1200 mg daily (serum level 0.8-1.3 mmol, only if chronic treatment is being considered) • Risperidone 2-6 mg daily • Valproate 1200-3000 mg daily (loading dose 20-30 mg/kg; serum level 75-100 mg; not preferred in women of childbearing age) • Ziprasidone 80-160 mg daily Treatment of acute depressive episode: • Best evidence: quetiapine 300-600 mg daily • Good evidence: fluoxetine/olanzapine combination therapy • Fair evidence: bupropion, fluoxetine, imipramine, sertraline, in combination with a antimanic agent; lithium monotherapy; lithium in combination with lamotrigine tranylcypromine, venlafaxine Maintenance treatment, best evidence for: • Aripiprazole • Lamotrigine • Lithium • Quetiapine
American Psychiatric Association (APA) (2002)**[69] **"This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"	Acute manic or mixed episodes • Adjunctive antipsychotic therapy should be considered in manic or mixed manic episodes with psychotic features • Second-generation agents are recommended over first-generation agents due to side effect profile Acute depressive episodes • Adjunctive antipsychotic therapy or electroconvulsive therapy is recommended in acute depressive episodes with psychotic features Maintenance • Adjunctive antipsychotic therapy should be closely monitored, reassessed and slowly tapered, if indicated Acute rapid cycling • Combination therapy with a second-generation antipsychotic may be indicated
National Institute for Health and Clinical Excellence (NICE) (2014)[74]	<u>Adults</u> Mania • Haloperidol, olanzapine, quetiapine or risperidone • Lithium alone or in combination with haloperidol, olanzapine, quetiapine or risperidone Depression • Fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine • Lithium alone or in combination with fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine Maintenance Therapy • Lithium alone or in combination valproate • Valproate, olanzapine, quetiapine

Guidelines	Recommendation
	Precautions There is an increased risk for side effects in young patients Antipsychotic treatment is not recommended for longer than 12 weeks in young patients For treatment of depression in young patients, a structured psychological intervention for at least 3 months is recommended Lithium and/or valproate should not be initiated in primary care Do not use lamotrigine for acute mania or mixed episode
American Academy of Child and Adolescent Psychiatry (AACAP) (2007)[71]	Standard therapy (based on adult literature): lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated; antidepressants may be used as adjunctive therapy for bipolar depression The choice of medication should be based on • Evidence of efficacy • Illness phase • Presence of confounding symptoms • Side effects • Patient's medication response history • Patient and family preferences Clozapine or electroconvulsive therapy are reserved for treatment-refractory cases Maintenance medication therapy may be recommended to prevent relapse Baseline and follow-up review of symptoms/efficacy, adverse effects and laboratory monitoring is recommended Trial of 6 to 8-week with a mood-stabilizing agent is recommended before switching agents or adding an additional agent Psychotherapy is recommended as part of a comprehensive treatment plan
Veterans Affairs/Department of Defense (VA/DoD) (2010)[76](2010)	Mania: • Agents most likely to be beneficial include lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone; lithium or valproate may be combined with an atypical antipsychotic Mixed episode • Agents most likely to be beneficial include valproate, carbamazepine, aripiprazole, olanzapine, risperidone or ziprasidone Depression • Agents most likely to be beneficial include quetiapine, lamotrigine, lithium, olanzapine/fluoxetine, olanzapine Treatment response should be evaluated at 4 to 8 weeks and periodically until full remission Patients who have failed monotherapy for mania: consider switching to another monotherapy or combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic

Guidelines	Recommendation
	Treatment of severe mania or mixed episode: clozapine with valproate or lithium Treatment of severe depression: clozapine
The Texas Medication Algorithm Project (TMAP) (2005)[77]	Hypomania Or Mania Stage 1 • Euphoric symptoms: lithium, valproate, aripiprazole, quetiapine, risperidone, ziprasidone • Mixed symptoms: valproate, aripiprazole, risperidone, ziprasidone Stage 1b • Olanzapine and carbamazepine are alternatives Stage 2 • Combination therapy with two: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics) Stage 3 • A different combination than in Stage 2, with additional options: carbamazepine, oxcarbazepine, aripiprazole, a first-generation antipsychotic Stage 4 • Clozapine or a 3-drug combination including lithium, an anticonvulsant mood stabilizer (valproate, carbamazepine, or oxcarbazepine) an atypical antipsychotic agent DEPRESSION Stage 1 • Lamotrigine monotherapy for patients without a recent and/or severe history of mania OR lamotrigine plus a mood stabilizer Stage 2 • Quetiapine monotherapy or olanzapine/fluoxetine combination treatment Stage 3 • Evidence-based medicine is limited

Migraine Prophylaxis

Migraines are the second most common type of headache, second only to tension headache.[78] The annual prevalence is higher in women (15%) than men (6%) which may reflect the increase in occurrence during the menstrual cycle.[78] Lost productivity and healthcare costs associated with migraine are $36 billion in the US. Healthcare costs for a family with a migraine sufferer are 70% higher than an unaffected family.[79] Migraine sufferers often have a positive family history and although migraines may begin at any age, the onset most often begins in childhood.[78] A diagnosis of migraine requires that attacks last 4-72 hours in patients in whom no other etiology is found. At least two of the following criteria must be present; unilateral pain, throbbing pain, aggravation by movement or moderate to severe intensity as well as either nausea/vomiting or photo- or phonophobia.[78] Attacks may be triggered by stress, hunger, bright lights, hormonal changes, lack of sleep, alcohol, chemical stimulation, bright lights or loud sounds.

Medications useful for the treatment of migraine include over the counter analgesics, prescription non-steroidal anti-inflammatory drugs (NSAIDs), 5-hydroxytryptamine-1 ($5\text{-}HT_1$) receptor antagonists, dopamine antagonists, butorphanol, the combination product containing acetaminophen-dichloralphenazone-isometheptene (Midrin®), and rarely opioids.[78] The selection of treatment is guided by consideration of whether the symptoms developed rapidly, if the

headache is a recurrence, if nausea/vomiting are present, if the headache is menses-related, if analgesics/NSAIDs have failed and whether oral intake is possible.[78]

Migraine prophylaxis may be considered if the migraine occurs with a predictable pattern as in menstrual migraine, occurs at a rate exceeding 2-3 episodes monthly, produces significant impairment, has not responded to symptomatic therapies or if therapy was associated with adverse effects or were considered intolerable by the patient.[80] The goal of migraine prophylaxis is to reduce the frequency, severity and duration of migraines, improve response to acute treatment, improve function and reduce disability.[81]

The American Academy of Neurology and the American Headache Society evidence-based guideline reviewed 29 Class I or Class II studies. They give a Level A (highest strength) recommendation for efficacy in the prevention of migraine attack and reduction in severity for divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol and timolol.[81] Frovatriptan was found effective in the prevention of menstrual migraine (Level A). Similar first-line prophylaxis recommendations were made by the Canadian Headache Society[82] and European Federation of Neurological Societies (EFNS)[83]

Pharmacology

Seizures are understood to result from abnormal, excessive, synchronous neuronal depolarizations.[2,3] Anticonvulsant medications exert their effects by blocking the initiation or spread of impulses via interaction with a number of possible sites or processes associated with the development of a seizure, including neurons, ion channels, receptors, glia, excitatory and inhibitory synapses. The goal of pharmacotherapy is to achieve a balance in postsynaptic potential between excitatory and inhibitory influences. Many older anticonvulsant medications do not have a precise mechanism of action defined. The most common mechanisms involved in anticonvulsant activity, for those compounds in which a mechanism is defined, include:[2,3,22,84,85]

1) interaction to block impulses at Na+ (sodium) ion channels. Active Na+ channels allow sodium to be transported into the cell and produce an action potential allowing the axon to fire. This is followed by the refractory period where the ion channel is inactive and during which the action potential cannot be propagated. Medications active at this site, stabilize the Na+ channel in an inactive state, preventing the development of an action potential and axonal firing. (e.g. carbamazepine, ethotoin, phenytoin, valproate).[4]

2) interaction at the GABA (γ-aminobutyric acid) receptor to enhance GABA activity. Gabaminergic activity is mediated at both GABA-A and GABA-B receptors. The GABA-B receptor is an active part of the potassium channel while GABA-A receptor stimulation facilitates the intracellular transport of chloride. Due to the negative charge of the chloride ion, the resting membrane potential is lowered making it more difficult for the cell to achieve an action potential. Medication activity at GABA sites, includes direct binding to GABA-A receptors, blocking presynaptic GABA reuptake, inhibiting GABA transaminase mediated GABA metabolism or increasing GABA synthesis (e.g phenobarbital, pentobarbital, primidone, valproic acid).

3) interaction at the voltage-gated Ca++ channel to inhibit impulse propagation. Three forms of calcium channels are known to exist (L, N and T). Activation of these channels allows calcium influx resulting in a partial depolarization of the cell membrane. Inhibition of these channels diminishes the development of an action potential. Medications that inhibit T-calcium

channels in the thalamus can stop absence seizures (e.g. carbamazepine, ethosuximide, phenytoin, valproate)

4) interaction with glutamate receptors to reduce cell excitation. Activation of the glutamate receptor results in the influx of sodium and calcium, and efflux of potassium ions which favors the development of an action potential. The glutamate receptor has 5-binding sites. Two of these sites are targeted by antiepileptic agents, the AMPA/kainite [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] site and the NMDA (N-methyl-D-aspartate) site (e.g. phenobarbital, pentobarbital).

5) interaction at the SV2A (synaptic vesicle glycoprotein 2A) protein ligand appears to stabilize the vesicle, reduce release of contents and decrease action potential-dependent neurotransmission.

6) interaction at potassium ion channels activates potassium currents which hyperpolarize the cells and stabilize the membrane.

7) interaction to inhibit carbonic anhydrase activity resulting in an increased intracellular concentration of hydrogen ions, reduction in pH and extracellular shift of potassium ions for acid-base balance. This results in cellular hyperpolarization and an increased seizure threshold (e.g. acetazolamide).

8) interaction to inhibit HCN (hyperpolarization-activated cyclic nucleotide-gated) channels, controlling Na+ and K+ currents, resting membrane potential, rhythmic activity of the brain and synaptic transmission (acetazolamide).

9) Agents active for petit mal (absence) seizures appear to suppress the three cycle per minute spike and wave activity that is associated with the loss of consciousness common in petit mal epilepsy (e.g. ethosuximide, methsuximide).

10) Inhibition of neuronal firing by reducing monosynaptic and polysynaptic transmission and increasing the threshold for electrical stimulation (e.g. primidone)

11) Reducing polysynaptic responses and post-tetanic potentiation (e.g. carbamazepine)

Pharmacokinetics

The ideal anticonvulsant medication is rapidly and completely absorbed with low plasma protein binding, is lipophilic to maximize central nervous system distribution, is minimally hepatically metabolized, does not interfere with the metabolism of other medications, is eliminated by the kidney and demonstrates linear elimination pharmacokinetics with a clear, dose-response relationship.[86-88] Unfortunately, most of the first-generation anticonvulsant medications lack many of these properties. Many of the agents are highly protein bound (acetazolamide, carbamazepine, primidone, valproate). All but acetazolamide are hepatically metabolized and carbamazepine, methsuximide, and primidone have active metabolites. Dosing can be complicated by non-linear pharmacokinetics with ethosuximide, ethotoin, pentobarbital and phenytoin. Unlike the newer anticonvulsant medications, most of the first-generation agents have established therapeutic serum/plasma concentrations associated with clinical efficacy.

Carbamazepine[88,89]: The metabolite is equipotent to the parent compound. This may enhance the therapeutic response in children who metabolize the drug more quickly than adults.[88]

Carbamazepine induces the enzymes responsible for its metabolism. This auto-induction results in lower plasma concentrations, a shorter half-life and increased clearance with chronic dosing.

Primidone[88,89]: The active metabolite, phenobarbital, has a much longer half-life than primidone. The concentration of phenobarbital may increase as the drug accumulates especially in patients with renal or hepatic dysfunction or the elderly who have age-related reductions in renal and hepatic function.

Valproic acid[88,89]: Concentration-dependent protein binding results in higher free drug concentrations with increasing doses such that plasma levels do not correlate with free drug levels. Additionally, valproic acid is a low extraction drug, meaning unbound drug is cleared. As plasma concentrations rise, the clearance of the free fraction is increased which may result in larger dosages yielding lower plasma concentrations.

Ethosuximide[88,89]: A good relationship exists between drug dosage and plasma levels. Children metabolize ethosuximide more rapidly than adults and often require higher dosages.

See **Table 7** for a comparison of the pharmacokinetics of the agents.

Table 7: Pharmacokinetics[6,7,88,90,91]

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life	Therapeutic Levels
Acetazolamide	Rapid Tmax Oral Tablet: 1-4 hr Oral ER Capsule: 3-6 hr	PB: 70-90% Vd: 0.2 L/kg	None	Renal: 90% (unchanged)	3-8 hr	N/A
Carbamazepine	BA: 89% For oral and extended release tablets compared to suspension Tmax: Oral ER tablet: 3-12 hr Oral Tablet: 4-5 hr Oral Suspension: 1.5 hr	PB: 76% Vd: 0.8-2 L/kg	Hepatic via CYP3A4 carbamazepine-10, 11-epoxide (CBZ-E) Metabolic auto inducer Children rapidly metabolized to equipotent CBZ-E	Fecal: 28% Renal: 72%	Initial: 26-65 hr After 3-5 weeks (auto-induction): 12-17 hr CBZ-E: 6.1 hr	Plasma: 4-12 mcg/mL
Ethosuximide	BA: 100% Tmax: 3-7 hr	PB: Low Vd: 0.7 L/kg	Hepatic via CYP3A4, CYP2E1 (minor) None active ***Non-Linear*** kinetics	Renal: 10-20% unchanged Renal, metabolites: 40-60%	Steady State: 4—7 days 25-60 hrs (adults) 30 (children)	Plasma: ~40-100 mcg/mL
Ethotoin	BA: unknown Tmax: 2 hr	PB: Low	Hepatic to inactive metabolites ***Non-Linear*** kinetics	Renal: Minimal	3-12 hr Plasma concentrations < 8mcg/mL: 3-9 hr Concentrations > 8mcg/mL: Non-linear	Plasma: 15-50 mcg/L
Methsuximide	BA: Well absorbed Tmax: 1-4 hr	N/A	Hepatic N-desmethylsuximide (levels > 700 x parent drug) with similar anticonvulsant activity. Can accumulate	Renal: <1%	1.4-4 hr N-desmethylsuximide Adult: 38 hrs Child:25.6 hr	Plasma: 10-40 mcg/mL
Pentobarbital	BA: 95% Tmax: within 15 minutes	PB: 45-70% Vd: 0.65-0.99 L/kg	Hepatic ***Non-Linear*** kinetics	Renal:<1% unchanged	15-48 hr	N/A
Phenobarbital	BA: 100%	PB: 40-50%	Hepatic and Renal None active	Renal: 25%	96 hr	10-40 mcg/mL

	Tmax 1-3 hr	Vd:0.75 L/kg				
Phenytoin	BA: 85% Tmax: 3-8 hr	PB: 90% Vd: 0.78 L/kg	Hepatic None active ***Non-linear*** kinetics	Renal: minimal	22 hr*	10-20 mcg/mL Free: 1-2 mcg/mL
Primidone	BA: 90-100% Tmax: 0.5-9 hr	PB: 25% Vd: 0.6-0.75 L/kg	Hepatic Phenobarbital Phenylethylmalonamide (PEMA)	Renal: 15- 64% unchanged PEMA: 6.6% Phenobarbital: 5.1%	10-12 hr PEMA 29-36 hrs Phenobarbital 53-140 hr	5-12 mcg/mL Phenobarbital: 15-40 mcg/mL
Valproic Acid and Derivatives	**BA:** 70-100% Depakote ER: 90% to IV Depakote ER: 89% to DR formulation **Tmax** Valproic acid DR capsule 2 hr fasted 4.8 hr fed Valproic acid capsule: 1-4 hr Depakote tablet or sprinkle: 4 hr Depakote ER: 4-17 hr Stavzor: 2 hr Rectal: 1-3 hr (off label) Divalproex: 4-6 hr Divalproex sprinkle capsule: 3.3-4.8 hr Divalproex ER: 4-17 hr Oral sodium valproate solution: 1.2 hr	PB 80-90% Free fraction @ 40 mcg/mL: 10% Free fraction @ 130 mcg/mL: 18.5% Vd valproate: 11 L/1.73 m^2	Hepatic	Urine: 30-50% <3% Unchanged	Varies by Age Newborns: 30-60 hr Neonates (in utero exposure): 40-45 hr Neonates < 10 days: 10-67 hr Children > 2 month: 7-13 hr Children. Adolescent 2-14 yr: 9 hr Adults: 9-19 hr	Epilepsy: 50-100 mcg/mL Acute mania: 50-125 mcg/mL ER tablets yield serum levels with 10-20% less fluctuation than DR tablet and are NOT bioequivalent

Key: BA=bioavailability; Tmax=time to maximum concentration; PB=protein binding; Vd=volume of distribution; CYP=cytochrome P450 hepatic microsomal enzyme; ER=extended-release

Therapeutic Drug Monitoring and Generic Substitution

The goal of treatment of epilepsy is to prevent or at least reduce the number of seizures while minimizing adverse events.[88] Plasma concentrations of older and many newer anticonvulsant medications are correlated with efficacy. Many of these medications have a narrow, therapeutic window separating seizure-reducing concentrations from adverse event and toxicity producing concentrations. A number of factors affect anticonvulsant medication concentrations, including adherence, genetic factors, differences in absorption, distribution, metabolism, elimination, timing of the laboratory sampling with respect to prior dosing, differences in bioavailability among different formulations or bioequivalent products, drug interactions, and whether metabolism involves saturable enzyme kinetics.[88] Traditionally, the use of therapeutic drug monitoring (TDM) has guided dosing of older anticonvulsant medications. A Cochrane Review in 2007 (updated 2010)[92] assessed the use and utility of TDM for antiepileptic medications in the treatment of epilepsy. A single, open study of 180 patients was found. Medications included, carbamazepine, valproate, phenytoin, phenobarbital and primidone. No difference was found between groups whether TDM was used or not, with respect to twelve-month remission rates (66% vs 61%, respectively), percent achieving seizure free status (56% vs 51%), or the percent reporting adverse eventss (48% vs 47%). This evidence does not support the widespread use of TDM, however, it may be useful in individual patients, those receiving polypharmacy or those with specific comorbidities.[92]

Generic substitution may affect intrapatient variability. The FDA allows generic to brand bioavailability differences of 20% in normal volunteers.[93] It is unknown whether patients with epilepsy differ in drug absorption resulting in individual drug concentration differences of greater than 20%. Issues affecting bioavailability, include water solubility, a narrow therapeutic range and nonlinear pharmacokinetics. Each of the three issues is pertinent to phenytoin and the first two to carbamazepine.[94] The American Academy of Neurology (AAN)[94,95] holds that safety and efficacy must be maintained. Switching from brand to generic should be done only when necessary and assessed with TDM.[94] Pharmacists should inform physicians of the opportunity for substitution along with the pertinent pharmacokinetic data, and the physician and patient should approve all generic substitutions. [94] The AAN is not in favor of economic considerations directing therapy or the implementation of prior authorization practices for newer or older anticonvulsant medications.[95] They do, however, support generic substitution for non-epilepsy use of these agents. A position paper by the ILAE[96] acknowledges a lack of evidence documenting clinical outcome differences in the treatment of epilepsy with branded or generic products. They believe anecdotal and clinical experience supports the utility of therapeutic drug monitoring to determine individual therapeutic concentrations. ILAE finds TDM is useful in defining toxicity, assessing compliance, guiding dosage adjustments, guide adjustments when interacting medications are required, to assist in managing phenytoin's dose-dependent pharmacokinetics. Taking a different stand, the FDA and American Society of Health-System Pharmacists support generic substitution.[97,98]

Yamada et al99, performed a systematic review of 20 studies assessing generic substitution of antiepileptic drugs in patients with epilepsy (prospective, n=6; retrospective n=7) and normal volunteers (n=7). The medications included lamotrigine, topiramate, carbamazepine, phenytoin and multiple undefined agents in 4 studies. Retrospective studies of lower quality (Class III) suggest use of generic products increases utilization of medical resources and switchback rates.

Prospective studies of lesser quality (Class II) in healthy adults found significant differences in carbamazepine pharmacokinetics. Small, good quality (Class I) prospective studies did not find a difference in pharmacokinetics or bioequivalence between generic and brand drugs in patients with epilepsy. The data suggests switching among multiple generics may be associated with greater pharmacokinetic variability and poorer clinical outcomes. They suggest consistency in the product selected, regardless of whether it is generic or brand and minimizing product substitution.

A systematic review and meta-analysis compared seizure control during epilepsy treatment with brand and generic equivalent antiepileptic drugs.[100] Evidence was found for phenytoin, carbamazepine and valproic acid. Their analysis of 7 randomized, controlled trials found an aggregate odds ratio for uncontrolled seizures with use of generic products to be 1.1 (95% CI 0.9-1.2). Results in observational studies (N=6) found an increase in switchback rates and drug or health services utilization attributed to brand-generic substitution differences that may reflect factors other than non-equivalence between brand and generic therapy. A second systematic review and meta-analysis[101] performed in 2002 identified 71 studies for qualitative analysis and 18 for quantitative analysis of innovator vs generic antiepileptic medications. Most data compared valproic acid, carbamazepine or phenytoin and was limited by small sample size, short duration of trials, low strength evidence and the lack of A-rated generic products. Overall, no differences were found between innovator and generic products for seizure occurrence (RR 0.87; 0.64-1.18) seizure frequency (standard mean difference SMD 0.03, -0.08-0.14), treatment failure (RR 1.02; 0.41-2.54), adverse events (RR 0.79; 0.28-2.20) or for pharmacokinetic determinations at maximum or minimum serum concentration or area under the curve.

Evidence suggests substituting brand for generic products is overall safe and effective. Caution should be used when substituting one generic product for another as there is greater risk for variability in serum levels. Therapeutic drug monitoring has a place in therapy for patients in which pharmacokinetic parameters may change (pregnancy); in medications with a narrow therapeutic window; to assess adherence; toxicity; or to assess the effects of the addition (or subtraction) of interacting medications.

Special Populations

Table 8 presents recommendations for use of these agents in special populations. Use of many of these medications in special populations requires caution.

Renal disease[6,88]: Renal disease is often associated with uremia and hypoproteinemia which result in reduced drug-protein binding and higher unbound, free levels which may increase adverse events or toxicity. Acid-base disturbances affect receptor sensitivity. Dialysis may affect albumin concentrations, protein binding or drug removal. Renal disease reduces the binding capacity of albumin which may increase the volume of distribution of phenytoin and valproic acid although free fractions remain constant and dosage adjustments are not required. The plasma half-life of phenytoin is reduced in renal disease by poorly defined mechanisms. Phenobarbital is partially eliminated renally and maintenance dosing in the setting of renal dysfunction are likely appropriate.

Hepatic disease[6,88]: Hepatic disease affects drug disposition by affecting protein binding, microsomal enzyme capacity and from hypoproteinemia. Protein binding alone does not affect

phenytoin or valproic acid disposition, however, in the setting of severe hepatic failure and cirrhosis plasma levels may increase and reductions in dosage may be required. Elimination of phenobarbital and pentobarbital is shifted renally in the presence of hepatic dysfunction and initial dosage reductions should be considered. Severe hepatic disease affects carbamazepine kinetics and plasma level determinations should guide dosage adjustments.

Pediatrics[6,88]: Newborns have lower protein binding capacity, higher free fatty acid and bilirubin levels with reduced hepatic microsomal enzyme activity, leading to higher free concentrations and longer half-lives of antiepileptic medications. In infants and children, microsomal enzyme activity often exceeds that of adults resulting in increased weight-based dosage requirements. In general, rates of absorption, protein binding, metabolism and renal elimination are lower in neonates than adults, while the free/unbound drug fraction and volume of distribution are increased. Infants demonstrate increased absorption and metabolism with lower protein binding resulting in higher free fraction of anticonvulsants.

Phenytoin kinetics are affected by age. Absorption is incomplete below 3 months of age. Kinetics are saturable in both children and adults. Children have increased metabolic enzyme capacity resulting in lower plasma concentrations, necessitating higher doses of phenytoin.

Phenobarbital bioavailability is reduced in infants and children due to lower gastric acid secretion and slower absorption than adults. Neonates exhibit lower protein binding with higher active, unbound concentrations. Metabolism is reduced in neonates, exceeds the rate of metabolism in adults at a few months of age (resulting in a shorter half-life and lower plasma concentration-dose ratio) and slows to adult rates by 10-14 years of age.

Primidone disposition is not well studied in newborns or infants, however, the pharmacokinetic parameters in children are similar to adults.

Carbamazepine metabolism is reduced in the newborn, increased in the infant and matches adults by childhood. Children have higher ratios of carbamazepine-epoxide-metabolite to carbamazepine concentrations which may play a more significant role as anticonvulsant in children than in adults. Equetro® (carbamazepine ER) has not been proven safe or effective in pediatrics or adolescents.

Valproic acid is metabolized more quickly in children resulting in a shorter half-life. Children less than 2 years of age have reduced hepatic elimination which may increase the concentration of toxic metabolites associated with hepatotoxicity. Children 3-10 years of age clear valproate 50% more rapidly than adults. Metabolism approximates that of an adult at 10 years of age.

Geriatrics[12,88]: Age affects many components of drug biotransformation. Absorption is often reduced. Body composition may affect the volume of distribution. Protein binding changes associated with age or concomitant declines in renal function result in a higher free fraction of drug. Finally, hepatic metabolism also declines. Adverse events associated with the use of antiepileptic drugs are common in the elderly due to these age-associated changes in drug biotransformation.[16-18] Clearance may be reduced by 20% for phenobarbital, 25% for phenytoin and up to 40% for carbamazepine and valproic acid.[17]

Other comorbid conditions or drugs may further affect biotransformation. Even though carbamazepine is the gold standard for treatment of partial seizures; valproate is the gold standard

for treatment of generalized seizures; phenobarbital and phenytoin are broad spectrum, inexpensive anticonvulsants, the use of these medications may be problematic in the elderly. Phenobarbital causes sedation, cognitive impairment, behavioral problems, enzyme induction and bone loss. Phenytoin use is associated with sedation, allergic reaction, non-linear kinetics, enzyme induction and bone loss. Carbamazepine is associated with neurotoxicity, allergic reactions, hyponatremia and bone loss. Valproate may cause tremor, weight gain, Parkinsonian symptoms, bone loss and enzyme induction.

Pregnancy[88]: Changes in the biotransformation of anticonvulsants in pregnancy may reflect the effects of estrogen and progesterone on hepatic metabolism. Gastrointestinal transit is slowed in pregnancy and may affect the rate and extent of absorption. The volume of distribution may be affected by changes in protein binding and intra- and extracellular fluid shifts. Dosage increases may be required for patients receiving phenytoin, carbamazepine, primidone and phenobarbital but should be guided by plasma drug level monitoring and reduced after delivery.

Teratogenicity: Children born to mothers with epilepsy have a higher incidence of stillbirth, microcephaly, mental retardation and seizure disorders. [102] Maternal tonic-clonic seizures are associated with fetal lactic acidosis, hypoxia and often lead to poor cognitive performance in childhood. Status epilepticus is linked with fetal death. Most major congenital abnormalities occur during organogenesis (8-10 weeks post conception) during which time the women may not know she is pregnant, and why contraceptive counseling is very important for women receiving antiepileptic therapy. The offspring of women receiving antiepileptic monotherapy have higher rates of congenital malformations (Odds Ratio 1.61; 95% CI, 1.18-2.19) than women who have not received antiepileptic therapy. The most common malformations include cleft palate, cleft lip and cardiac abnormalities.[102]

Since the 1960's fetal effects associated with the use of antiepileptic drugs have been reported.[103] Antiepileptic drugs may be associated with higher spontaneous abortion rates for which folic acid appears to be protective.[104,105] All women of child-bearing age receiving anticonvulsants should be offered folic acid.[102] Reported malformation rates are higher with valproate and phenobarbital than with carbamazepine or newer antiepileptic medications. The risk of malformation is highest with the use of combination therapy that includes valproate, but is elevated with all polypharmacy-antiepileptic-drug-regimens. Specific abnormalities are associated with each agent. Valproate is associated with neural tube defects, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis. Carbamazepine is associated with neural tube defects at 1/4 the incidence with valproate (0.5% vs 2.0%, respectively). [102,105,106] Phenytoin is associated with fetal-hydantoin syndrome resulting in craniofacial defects and 2 of the following prenatal or postnatal growth deficiency, limb defects, major malformations or mental deficiency.[107] With the exception of valproate, the risk to the mother and fetus appear to be lower with vs without anticonvulsant therapy during pregnancy. Recommendations include pre-pregnancy counseling and conversion to optimal monotherapy of a lower-teratogenic risk medication before pregnancy. No changes are recommended to established therapy if a woman is found pregnant. Treatment should be at the lowest effective anticonvulsant dose, include therapeutic drug monitoring during pregnancy, include folate supplementation and encourage participation in the Antiepileptic Drug Pregnancy Registry.[108]

Genetic variability[6,109]: Phenytoin and carbamazepine should be avoided in patients who carry the HLA-B*15:02 gene (carrier status). Most of these people are of Chinese or South East

Asian descent. They are at significantly increased risk of developing potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis.

Dose adjustments in non-carriers should be based on CYP2C9 phenotype status. For instance, in adults categorized as intermediate metabolizers the initial maintenance dose of phenytoin should be reduced by 25% and by 50% for poor metabolizers with therapeutic drug monitoring guiding further dosing adjustments. Pediatric patients with intermediate or poor CYP2C9 metabolizer status may require TDM to determine optimal dosing.

Drug Specific Special Population Information

Phenytoin is highly protein bound, primarily to albumin. Hypoalbuminemia may occur in the elderly, in cachexia, in nephrotic syndrome, hepatic cirrhosis and inflammatory disorders.[110] Changes in albumin concentrations can significantly affect concentrations. Dosage adjustments are recommended utilizing the following formula[6,109]:

$$\textit{Normal concentration (in hypoalbuminemia)} = \frac{\textit{observed phenytoin concentration}}{\textit{[(0.25 x albumin concentration) +1.0]}}$$

Carbamazepine[88,6,109]: The metabolite, carbamazepine epoxide, is equipotent to the parent compound. This may enhance the therapeutic response in children who metabolize the parent drug more quickly than adults.[88] Carbamazepine induces the enzymes responsible for its metabolism. This auto-induction results in lower plasma concentrations, a shorter half-life and increased clearance with chronic dosing. Auto induction steady state is achieved by 3-5 weeks of therapy.

Primidone[88,6,109]: The active metabolite, phenobarbital, has a much longer half-life than primidone. The concentration of phenobarbital may increase as the drug accumulates especially in patients with renal or hepatic dysfunction or the elderly who have age-related reductions in renal and hepatic function and are more sensitive to the effects of central nervous system depression.

Valproic acid[88,6,109] Valproic acid is a low extraction drug meaning unbound drug is cleared. Concentration-dependent protein binding results in free drug concentrations increasing with increasing doses, thus plasma levels do not correlate with free drug levels. As plasma concentrations rise, the clearance of the free fraction is increased. Clinically, larger doses may be paradoxically associated with lower plasma concentrations.

Ethosuximide[88,6,109]: A good relationship exists between drug dosage and plasma levels. Children metabolize ethosuximide more rapidly than adults and often require higher dosages.

Table 8: Special Populations [6,88,109,110]

	Renal	Hepatic	Pregnancy	Lactation Crosses	Pediatric	Geriatric	Other
Acetazolamide	CrCl > 50 mL/min administer every 6 hr CrCl 10-50 mL/min administer every 12 hours CrCl <10 mL/min not recommended Dialysis may require supplementation	Caution: may cause precoma/coma	C	Yes Consider the risk:benefit of therapy	None	Glaucoma • 125 mg four times daily • 500 mg sustained release once daily	None
Carbamazepine	None	Any dysfunction consider dose reduction Aggravated liver dysfunction or active liver disease, not recommended	D	Yes Minimal risk	None	None	None
Ethosuximide	Use with caution	Use with caution	N	Yes Consider the risk:benefit of therapy	None	None	None
Ethotoin	None	Contraindicated	D	Yes Consider the risk:benefit of therapy	None	Reduce initial dose	None
Methsuximide	None	Use with caution	N	Unknown	None	None	None
Pentobarbital	Dose reduction recommended	Dose reduction recommended	D	Yes Consider alternate therapy	Caution in debilitated patients	Reduce initial dose Caution in debilitated patients	None
Phenobarbital	Mild-to-moderate dysfunction: No change Severe renal dysfunction (CrCl <10 mL/min)	Contraindicated in the presence of significant hepatic dysfunction	D	Yes Consider the risk:benefit of therapy	Caution in debilitated patients	Reduced dosage due to prolonged half-life, delayed hepatic biotransformation, increased drug sensitivity	Increased doses for status epilepticus, psychosis, excitement, insomnia Max: 600 mg/24 hr

	Renal	Hepatic	Pregnancy	Lactation Crosses	Pediatric	Geriatric	Other
	administer every 12-16 hours Caution: Long-term accumulation Dialysis requires dosage supplementation	Caution with mild-to-moderate dysfunction Reduce initial doses					
Phenytoin	None High-efficiency dialyzers may require supplemental doses	None (See text)	D	Yes Consider Alternate therapy	None	Lower or less frequent dosing Immediate Release: • Initial dose 3 mg/kg/day in divided doses	Pregnancy dose increase required lower after delivery Trauma - higher doses often required over 7-10 days Hypoalbuminemia (see text) Obesity - higher doses may be required, consider TDM
Primidone	CrCl > 50 mL/min Dose every 8 hr CrCl 10-50 mL/min Dose every 8-12 hr CrCl < 10 mL/min Dose every 12-24 hr Dialysis required supplemental dose	Caution in severe liver disease	D	Yes Consider the risk:benefit of therapy	None	None	None
Valproate derivatives	None	Do not use with hepatic disease or hepatic insufficiency	X	Yes Consider the risk:benefit of therapy	Concomitant Rufinamide Add valproate to rufinamide at initial doses < 10 mg/kg daily	Reduce initial dosage Titrate slowly Monitor fluid and nutritional intake, dehydration, somnolence	Concomitant use of Rufinamide (adults) • Add VPA at lower dose and titrate • <400 mg/day adults

Methods

A literature search was conducted to identify articles evaluating long-acting opioid agents, searching the MEDLINE database (1950 – 2016), EMBASE database (1966-2016), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English, evaluating the efficacy of the older anticonvulsant agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included.

Clinical Evidence

Ethosuximide vs Valproic Acid (vs Lamotrigine) in Childhood Absence Epilepsy

Glauser et al[111] conducted a 16-week, randomized, double-blind, controlled trial in 453 children with absence epilepsy. Patients received either ethosuximide, valproic acid (each up to 60 mg/kg) or lamotrigine (up to 12 mg/kg). Modified intent-to-treat analysis found more patients receiving lamotrigine received maximum dose therapy than ethosuximide or valproic acid (58.9% vs 17.5% vs 20.5%, respectively). At the completion of the study, the overall freedom from failure rate was 47%. The rate of response was not different between ethosuximide and valproic acid 53% and 58% respectively (p=0.35) which performed better than lamotrigine (29%; p<0.001 for each). No difference was found between groups for discontinuation rates due to adverse events, however, valproic acid was associated with more attentional dysfunction than ethosuximide, 49% vs 33% respectively (odds ratio 1.95, 95% CI 1.12-3.41; p=0.03).

A 12-month follow-up study by the same investigators[112] included 446 patients. The overall freedom from failure rate was 37%. Again, no difference was found between treatment with ethosuximide or valproic acid (45% vs 44%, respectively; OR 0.94, 95% CI 0.58-1.52, p=0.82) and each performed statistically superior to lamotrigine (21%; p<0.001). A lack of seizure control was found in more patients treated with lamotrigine (p<0.001 than ethosuximide or valproic acid. Discontinuation rates due to intolerable adverse events were more common with valproic acid (p<0.01) than ethosuximide or lamotrigine and included negative effects on attentional measures, weight gain, digestive disorders, fatigue, headache, laboratory abnormalities or rash. The authors conclude that ethosuximide is the optimal initial treatment for childhood absence epilepsy.

Childhood absence epilepsy is associated with the long-term occurrence of generalized tonic-clonic seizures in 30-60% of children.[113] Shinnar et al[113] reported on the cohort of children treated in the Glauser trials of 2010[111] and 2013[112] at a median followup of 7.0 years to assess the development of generalized tonic-clonic seizures. The incidence of generalized, tonic-clonic seizures in the cohort was 12% at a median time of 4.7 years (interquartile range, IQR, 2.3-6.3 years) and median age of 13.1 years. Twenty-eight percent of the patients were no longer receiving anticonvulsant therapy. Univariate analysis found a number of factors associated with the development of generalized, tonic-clonic seizures including older age at enrollment. The 5-year risk when enrolled at age ≥9 years was 19% (95% CI, 12%-28%; p=0.0009), for 7-8 year olds 5-year risk was 6% (3%-13%; p=0.03) and for those ≤6 years it was 3.9% (1.7%-8.5%; p=0.0003). Risk was increased for those patients with shortest duration of burst on baseline electroencephalogram (EEG) recording (p=0.037). Initial treatment with either ethosuximide or valproate or lamotrigine was not statistically associated with the development of generalized tonic-clonic seizures, however, failure of initial treatment at week 16-20 visit was associated with the development of generalized, tonic-clonic seizures (p<0.001). When evaluated by medication,

initial treatment failures with ethosuximide (p<0.0001) and valproate (p=0.017), but not lamotrigine (p=1.0) were associated with the development of generalized, tonic-clonic seizures. Conversely, patients who responded to initial therapy with ethosuximide were the least likely to develop generalized, tonic-clonic seizures over time regardless of whether the patient was continuing ethosuximide or had their treatment changed to ethosuximide after the initial 16-20 weeks. On multivariate analysis these findings persisted. When randomization age was included in the analysis, the EEG short burst finding was no longer significant. The yearly risk by harms ratio (HR) of developing a generalized, tonic-clonic seizures was approximately 20%. Overall, patients who respond to initial therapy with ethosuximide are least likely to develop generalized, tonic-clonic seizures.

An updated Cochrane Review[114] in 2005 found only 5 studies which compared ethosuximide or sodium valproate or lamotrigine for the treatment of absence seizures in children and adolescents. Trials suffered from poor methodology and a lack of power. One study compared lamotrigine to placebo and found lamotrigine better than placebo at maintaining seizure freedom. Three trials compared ethosuximide to valproate and found no difference in seizure freedom or the achievement of a >50% or >80% reduction in seizure frequency. The final study compared valproate to lamotrigine. Although no difference in seizure freedom was found at 12 months, valproate was much more rapidly acting with 52.6% of participants' becoming seizure free with one-month of valproate therapy vs 5.3% of those receiving lamotrigine. No serious or unusual adverse events occurred with any of the treatments.

> *Summary: Four Cochrane Reviews have assessed the efficacy and safety of valproic acid, ethosuximide and lamotrigine. Ethosuximide and valproic acid appear to be equally efficacious and each statistically more efficacious than lamotrigine in the treatment of childhood absence epilepsy with valproic acid producing a therapeutic effect more rapidly than lamotrigine. These findings were confirmed in short-term, 12-month and long-term trials. With respect to safety, valproic acid treatment was associated with more discontinuations due to adverse events, including higher rates of negative attentional measures and weight gain. A failure of ethosuximide or valproic acid therapy at ~16-20 weeks of treatment is predictive of the long-term development of generalized, tonic-clonic seizures, while an initial, 16 to 20-week positive response to ethosuximide therapy identified patients least likely to develop generalized, tonic-clonic seizures with long-term therapy. Overall, in the setting of absence epilepsy of childhood ethosuximide appears to offer the best efficacy and safety.*

Phenytoin vs Valproate in Generalized and Partial Epilepsy

A Cochrane Review[115] compared phenytoin and valproate monotherapy in the treatment of partial and generalized epilepsy (excluding myoclonus and absence seizures). This individual patient data review identified 11 trials with 1119 patients. Individual patient data was available for 699 patients in 5 trials and did not include the other 6 trials of 450 patients. A major confounding factor in this (and any) epilepsy trial is the potential for misclassification of a patient's seizure type. Evidence reflecting patient followup at 1-91 months was presented as harms ratios (HR; 95% confidence interval). Retention time, stratified by seizure type, non-statistically favored valproate (HR 1.09; 0.76-1.55). Phenytoin was non-statistically superior to valproate (HR of 0.98; CI 0.59-1.64) for retention time in generalized onset seizures. Valproate was non-statistically superior to

phenytoin for retention time in partial onset seizures (HR 1.20; 0.74-1.95). The time to achieve a 12-month remission free period, non-statistically favored valproate (HR 0.98; 0.78-1.23) when stratified by epilepsy type. For generalized onset seizures, phenytoin was non-statistically superior to valproate (HR 1.04, 0.77-1.40), while valproate was non-statistically superior to phenytoin for partial onset seizures (HR 0.90; 0.63-1.29). Time to achieve a 6-month seizure free period was not statistically different but did favor valproate over phenytoin for each measure; stratified by seizure type (HR 0.95; 0.78-1.15); for generalized onset seizures (HR 0.92; 0.72-1.18) and for partial-onset seizures (HR 0.99; 0.73-1.35). Finally, the time to first, post-randomization seizure was not significantly different between phenytoin and valproate; when stratified by seizure type, favoring phenytoin (HR 0.93; 0.75-1.14); for generalized-onset seizures favoring valproate (HR 1.03; 0.77-1.39) and for partial onset seizures favoring phenytoin (HR 0.83; 0.62-1.11).

A randomized, controlled trial compared the efficacy of intravenous valproate vs phenytoin in 100 children age 3-12 years presenting to an emergency department with acute motor focal or generalized seizures (second episode).[116] Children convulsing at presentation were given intravenous (IV) diazepam. Children received 20 mg/kg IV loading doses of valproate or phenytoin followed by maintenance doses. There were no differences in the percentage of children presenting with convulsions or unconscious. The primary outcome, control of seizures for 24 hours was not different between treatment groups (p=0.345). No difference was observed in the time to seizure cessation (p=0.90). Therapeutic drug levels were similarly achieved at 4 and 24 hours with valproate or phenytoin (p>0.05). No differences were found in cardiorespiratory parameters (heart rate, respiratory rate, blood pressure or oxygen saturation) within or between treatment groups (p>0.05). The only statistically different finding was the time for regaining consciousness in children that presented unconscious to the emergency department, for valproate 58.33 ± 28.50 minutes vs phenytoin 135.00 ± 62.10 minutes (p=0.010).

Summary: The evidence finds no difference between phenytoin and valproic acid in the setting of partial and generalized epilepsy (excluding myoclonus and absence seizures) in adults and children for a variety of outcome measures. No difference was found between intravenous valproate or phenytoin in an emergency room setting of children with acute motor focal or generalized seizures, although unconscious children regained consciousness significantly more rapidly with valproate.

Phenytoin vs Carbamazepine

A Cochrane Review[117] compared phenytoin and carbamazepine monotherapy for the treatment of partial onset or generalized seizures in children and adults. A total of 12 trials were identified, of which 4 trials (N=595) included individual participant data and were included in the review. Trials were of overall good quality although the authors suggest that up to 30% of patients may have had their seizure type misclassified. Outcome measures included time to 6-month remission, time to 12-month remission, time to first seizure post randomization and time to treatment withdrawal as a measure of tolerability. Follow-up ranged from 1 day to over 4400 days. No significant difference was found in any outcome measure between phenytoin and carbamazepine including serious adverse events. Treatment with phenytoin was associated with a lower early withdrawal rate. Adverse events reflected the product labeling with no serious or unusual events noted.

Summary: Limited evidence which may be confounded by misclassified seizure type, finds no difference in efficacy between phenytoin and carbamazepine for

efficacy measures in children and adults with partial onset or generalized seizures. Carbamazepine use resulted in a higher discontinuation rate, suggesting lower tolerability.

Phenobarbitone/Phenobarbital vs Phenytoin

A Cochrane Review[118] compared phenobarbitone vs phenytoin for monotherapy treatment of generalized, tonic-clonic seizures or partial onset seizures in adults of children. Individualized participant data was found in 4 of 8 identified trials for 599 participants reflecting 63% of the data. Care must be taken when interpreting the skewed data with 78% of participants having partial onset seizures and 22% generalized seizures. For every measure of time to treatment withdrawal (pooled participants, pooled by seizure type or stratified by seizure type) phenobarbitone treatment resulted in statistically more withdrawals than phenytoin. The time to 6- and 12-month remission did not differ between the two groups, however, summary statistics with wide confidence intervals do not support equivalence. The time to the first, post-randomization seizure did not differ between treatment groups. Overall, no difference in seizure control was identified between phenobarbitone and phenytoin although phenytoin therapy resulted in significantly fewer treatment withdrawals which may reflect better tolerability.

Painter et al[119] compared phenobarbital and phenytoin when dosed to predetermined serum concentrations in 59 neonates with seizures. Neonates not responding to treatment were treated with combination therapy. Phenobarbital and phenytoin monotherapy produced similar rates of EEG proven complete seizure control (43% vs 45%, respectively; p=1.0). Combination therapy resulted in similar results regardless of whether the patient received phenobarbital or phenytoin initially (57% vs 62%, respectively; p=0.67).

Summary: The evidence suggests that phenobarbitone and phenytoin are not different in efficacy outcomes for neonatal seizures. Although response rates were not statistically different, the evidence is insufficient to prove equivalence in the treatment of generalized, tonic-clonic and partial seizures in adults and children with phenytoin better tolerated.

Carbamazepine vs Valproate

Marson et al[120] performed a meta-analysis comparing valproate and carbamazepine therapy in the treatment of epilepsy in children and adults in which a misdiagnosis of epilepsy could not be ruled out. Assessed outcomes included the retention time, time to first post-randomization seizures and time to 12-month remission. In the setting of generalized-onset seizures no difference was found between treatments. In the setting of partial-onset seizures the evidence for time to 12-month remission (HR 0.82; 95% CI 0.67-1.00) and time to first post-randomization seizure (HR 1.22; 1.04-1.44) supported carbamazepine as at efficacious as valproate for first-line therapy of partial-onset seizures.

Summary: Evidence, which may be confounded by misclassified seizure type, finds both carbamazepine and valproate were equally efficacious in the treatment of generalized and partial-onset epilepsy in adults and children.

Methsuximide

Methsuximide was prospectively studied in an open-label protocol of 112 children with epilepsy refractory to first line antiepileptic drugs or combinations or antiepileptic drugs.[121] At 9 weeks of therapy, 35.7% of patients experienced a ≥50% reduction in seizure frequency. The benefits persisted in 19.6% of patients for more than 3 years. Adverse events were mild (hiccups, nausea, vomiting, drowsiness) with 10.7% discontinuing therapy due to adverse events. Methsuximide serum concentrations were positively correlated with reversible ataxia and leukopenia when >45 mg/L.

Tennison et al[122] found methsuximide efficacious when added to the current regiment of children with intractable epilepsy on maximal, combination therapy. A reduction in seizure frequency was achieved in >50% of children and was maintained for a mean of 19 months although no patient achieved complete seizure remission. A single patient's seizures worsened on therapy.

Dasheiff et al[123] compared clorazepate, methsuximide and valproate treatment in 66 patients with medically refractive, complex partial seizures with secondary generalization or partial seizures with aura who failed phenytoin, carbamazepine or phenobarbital therapy. The frequency of seizures were non-significantly reduced with each therapy. The elimination of seizures with tolerated side effects occurred in small numbers of patients similarly with each medication. Adverse events were rare with clorazepate. Methsuximide and valproate use resulted in gastrointestinal and mental status changes and valproate therapy resulted in impaired coordination.

Summary: In children and adults with refractory epilepsy who failed therapy with multiple medications, limited, low quality evidence suggests methsuximide can reduce the seizure frequency in ~ 1/3 of patients, although the effects do not appear to be long-lived. A small trial suggests methsuximide efficacy may compare favorably with clorazepate and valproate. Methsuximide is associated with gastrointestinal toxicity and mental status changes and at least some of methsuximide adverse effects are dose related (ataxia, leukopenia).

Acetazolamide

Acetazolamide was assessed for utility as adjunct therapy in 37 Japanese children with refractory epilepsy complicated by mental retardation currently failing therapy to a combination of at least two of the following medications, carbamazepine, clonazepam or sodium valproate[124]. Acetazolamide therapy was initiated at 10 mg/kg and increased to 20 mg/kg as indicated. No relationship was found between drug dosage or steady state serum concentrations and efficacy. A complete remission persisting > 3 years was observed in 4 patients with localization-related epilepsies. Remission persisting 6 months followed by failure was reported for 5 patients, 6 patients demonstrated a reduction in seizure frequency of at least 50%, and 22 patients did not respond to acetazolamide therapy. The medication combination of acetazolamide with clonazepam and carbamazepine performed statistically superior to other combinations (p=0.05). Acetazolamide was well tolerated with transient drowsiness common during the initiation of therapy. One patient reported passing a rice-grain-sized kidney stone during his 6th year of effective acetazolamide therapy.

Summary: Evidence suggests acetazolamide has utility as adjunctive therapy in refractory epilepsy. The combination of acetazolamide, clonazepam and carbamazepine performed statistically superior to other combinations. Although 60% of children did not respond to

therapy it is important to remember that the average non-response to antiepileptic therapy overall is 20-30% and demonstrating a benefit in 40% of difficult to treat, refractory, patients with mental retardation is important. Acid-base induced kidney stones are a potential complication of acetazolamide therapy, only one patient treated for 6+ years reported passing a stone. Acetazolamide was well tolerated with Transient drowsiness was the most common adverse event.

Status Epilepticus

There are currently no class I clinical trials which compare second-line therapy for status epilepticus. Agents recommended in practice guidelines include benzodiazepines, barbiturates, phenytoin/fosphenytoin, valproic acid, levetiracetam, thiopental and propofol.[54] The Established Status Epilepticus Trial[125] is an ongoing, prospective trial comparing fosphenytoin, levetiracetam and valproic acid for the treatment of status epilepticus. It aims to address the efficacy and tolerability of currently available treatments for established status epilepticus.[125] A systematic review and common, reference-based, indirect comparison meta-analysis[126] was performed on 3 previously performed published meta-analyses (N=287). Intravenous valproate was compared to intravenous phenobarbital by indirect comparison from two systematic reviews of intravenous phenytoin vs valproate and one systematic review of intravenous phenytoin vs phenobarbital. Clinical seizure cessation occurred with an OR of 1.0 (0.36-2.76) for the comparison of intravenous phenobarbital vs valproate. Fewer adverse events were found with valproate than phenobarbital (OR 0.17; 0.04-0.71) although this did not achieve statistical significance. Direct meta-analysis results of valproate vs phenytoin found no significant difference in clinical seizure reduction (OR 1.81; 0.60-5.52) while valproate use produced statistically fewer adverse events (OR 0.22; 0.06-0.87). In direct comparison of phenobarbital vs phenytoin, no statistical difference was found for clinical seizure cessation (OR 1.81; 1.02-3.20) or adverse events (OR 1.32; 0.75-2.34). The most common adverse events included respiratory depression and liver dysfunction with phenytoin and valproate, hypoventilation and arrhythmias with phenobarbital and phenytoin and hypotension with phenytoin.

Malamiri et al[127] performed a RCT in 60 children ≥ 2 years with status epilepticus uncontrolled by IV diazepam. Treatment included IV valproate or phenobarbital and efficacy was defined as a cessation of seizing within 20 minutes of starting treatment. No difference was found in achieving a seizure-free status within 20 minutes. Prevention of seizure recurrence within 24 hours after initial seizure control was statistically superior with valproate (p=0.007). Valproate also produced significantly fewer adverse events (p<0.001); of note, phenobarbital treatment was associated with a greater frequency of more lethargy (17/30 vs 3/30 patients).

Treiman et al[128] compared 4 treatments (diazepam/phenytoin, lorazepam, phenobarbital or phenytoin) in overt or generalized, convulsive status epilepticus in adults. In patients with a verified diagnosis of overt status epilepticus, lorazepam was found superior to phenytoin (p=0.002) in producing a cessation of seizure activity within 20 minutes which persisted for 40 minutes. Of interest, the time required for complete infusion of lorazepam was significantly shorter than for all other regimens and significantly longer for phenytoin regimens (approximately 5 minutes for lorazepam vs 33 minutes for phenytoin). In an intent-to-treat analysis including patients with verified and unverified status epilepticus, no difference was found between treatment groups. Adverse events were similar with all medications.

Summary: Evidence suggests that for the treatment of status epilepticus, valproate, phenobarbital and phenytoin are equally efficacious. It is unclear if lorazepam provides superior efficacy to other treatments, or is more quickly effective because it can be administered more rapidly. Treatment with valproate was associated with fewer adverse events than with phenobarbital and statistically fewer events than phenytoin, while phenobarbital and phenytoin use resulted in similar rates of adverse events. For each agent the adverse events paralleled the prescribing information. For uncontrolled status epilepticus valproate maintains a 24-hour, seizure-free state better than phenobarbital with statistically fewer significant adverse events.

Bipolar Illness

Divalproex ER was found more effective than placebo in reducing hypomania/mania symptoms of bipolar illness when initiated with an oral loading dose.[129] At 8 weeks, reductions were noted in Young Mania Rating Scale (YMRS) score (p=0.024), clinical global impression-bipolar (CGI-BP) overall (p=0.044) and CGI-BP mania scores (p=0.047). The adverse event rates and discontinuation rates did not differ between groups although the study was confounded with significant study attrition (43%). In contrast, Hirschfelt et al[130] found no difference between treatment with divalproex ER and placebo at 8 weeks in adults with bipolar I disorder (manic or mixed) for any outcome measure. Adverse events did not differ significantly between groups except for more back pain and constipation in the divalproex group. Serious adverse events requiring hospitalization occurred in two patients receiving divalproex ER (depression and overdosage) and one patient receiving placebo (edema).

Stoner and Dahmen[131] published a comprehensive review and critical analysis of trials using extended-release divalproex and delayed-release divalproex in bipolar disorder. Their review of three small, open-label trials of extended-release (ER) divalproex and 3 data sets from Letters to the Editor to be limited by short durations, lacking in power, methodology and sample size. They found the limited evidence useful in presenting "practical practice information". Studies in which divalproex DR was converted to the ER formulation included some converting to equivalent doses and some converted mg-for-mg. Converting mg-for-mg resulted in higher valproic acid serum concentrations that remained within the therapeutic range for more than 95% of patients. Overall, the limited evidence found no efficacy advantage or safety disadvantage to use of divalproex ER compared with the DR formulation. The lower peak concentration may reduce dose-related (Cmax) adverse events and once daily dosing may improve adherence to therapy.

Joshi et al[132] performed an open-label trial of extended-release (ER) carbamazepine in children with bipolar disorder having manic, hypomanic or mixed symptomatology. Carbamazepine ER significantly ($p \leq 0.001$) reduced manic symptoms at 2 at 8 weeks and produced significant improvements in Clinical Global Assessment for depression (43%; p=0.001) and psychosis scores (62%; $p<0.001$). A remission of mania was achieved in 34% of patients at 8 weeks. Overall, adverse events mirrored the prescribing information. A marginal, significant increase in body weight of 0.8 kg was observed with carbamazepine ER. Carbamazepine ER therapy was associated with prolongation of PR and QRS intervals (p=0.001 and p=0.04, respectively). Two patients receiving carbamazepine developed skin rashes which abetted upon medication discontinuation.

Summary: Although most clinical practice guidelines consider valproic acid appropriate for first-line treatment or maintenance therapy in bipolar disorder with manic or mixed

symptomatology, the evidence is conflicting. One small trial confounded with a significant valproate ER attrition rate, found valproate ER statistically superior to placebo while a larger trial of shorter duration failed to find a difference between valproate ER and placebo. Adverse and serious adverse events were not significantly different. A critical appraisal of valproate ER and DR suggests equivalent efficacy with a theoretical advantage for the ER formulation to minimize concentration-dependent adverse events and afford a once-daily dosing advantage. Carbamazepine ER is efficacious in the treatment of bipolar disorder although 2 of 27 patients developed a rash and carbamazepine ER was statistically associated with increases in the PR and QRS interval and modest weight gain.

Migraine Prophylaxis

A Cochrane Review[133] of valproate for prophylaxis of episodic migraine in adults reviewed 10 trials of 848 patients. Valproate was found efficacious for this indication. Headaches were reduced by a mean of 4 per month when compared with placebo therapy (mean difference, MD, -4.31 (95% confidence interval, -8.32 to -0.30). More than 50% of patients experienced a ≥50% reduction in headache frequency with divalproex vs placebo. Propranolol and valproate were similarly efficacious while topiramate offered a slight but significant advantage over valproate. Treatment with valproate and divalproex was well tolerated although associated with significant nausea.

Summary: Evidence supports the efficacy and safety of valproic acid derivatives for the prophylaxis of migraine.

Safety:

Black Box Warnings[6,7,134]

Carbamazepine use may result in serious or fatal dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Risk is greatest in people of Asian descent with the inherited allelic variant HLA-B*1502. All patients at risk, should have genetic screening before initiating carbamazepine therapy and patients testing positive should not receive the drug. Other serious adverse events include agranulocytosis and aplastic anemia. Pretreatment and periodic hematologic monitoring should be obtained and if bone marrow depression occurs, consider drug discontinuation.

Phenytoin The rate of intravenous administration should not exceed 50 mg/min in adults, or the slower of 1-3 mg/kg/min or 50 mg/min in children to avoid hypotension and cardiac arrhythmias. Some experts recommend even slower administration rates.

Valproic Acid/Divalproex/Valproate Sodium: An increased risk of potentially fatal hepatotoxicity within 6 months of drug initiation has occurred in children <2 years of age, especially in children with mitochondrial DNA polymerase gamma (POLG) gene mutations. Other possible risk factors include severe seizure disorders, mental retardation and organic brain disease. Hepatic function should be monitored especially during the first 6 months of treatment. Failure of other therapies is the only valid indication for use of valproate in young children. Impaired cognitive development and major congenital malformations (neural tube defects) limit the use of valproate in women of child-bearing age. Life-threatening pancreatitis has occurred in adults and children and children may experience a loss of seizure control with valproate therapy.

Contraindications[6,7,134]

All the agents included in this review are contraindicated for hypersensitivity to the medication. Barbiturates, pentobarbital, phenobarbital and primidone are contraindicated in patients with a history of manifest or latent porphyria. Phenobarbital and pentobarbital are contraindicated in significant liver dysfunction or respiratory disease with dyspnea or obstruction. Of the hydantoin class of anticonvulsant medications, phenytoin is contraindicated in combination with delavirdine. Ethotoin is contraindicated for use in patients with hepatic abnormalities or hematologic disorders. Acetazolamide is contraindicated in people with sulfonamide sensitivity. It should not be used in hypokalemia, hyponatremia, with marked kidney, liver disease, dysfunction or hepatic encephalopathy, in suprarenal gland failure, hyperchloremic acidosis. Long-term use should be avoided in patients with chronic, noncongestive angle-closure glaucoma. Carbamazepine use is contraindicated with nefazodone, monoamine oxidase inhibitors and in patients with a history of bone marrow depression. Valproic acid derivatives should not be used in people with urea cycle disorders or hepatic dysfunction.

Adverse Effects:

Drug-induced adverse events significantly, deleteriously impact the treatment and outcomes of patients with epilepsy. Antiepileptic drug therapy intolerance results in the discontinuation of therapy in 10-30% of people with epilepsy.[135] Depending on the method of assessment, 10-95% of patients receiving long-term antiepileptic experience adverse events. In patients with resistant epilepsy, quality of life is more highly affected by poor drug tolerability than seizure frequency.[135] The adverse events of the various agents are summarized in **Table 8.**

Neurologic adverse events include sedation, fatigue, dizziness, impaired coordination, cognitive defects, tremor, mood or behavioral changes and sexual dysfunction.[1,2,5-7,109,135,136] Carbamazepine and phenytoin may exacerbate seizures.[43,135]

Idiosyncratic adverse events may occur with carbamazepine, phenytoin, barbiturate or valproic acid therapy.[6,7,135] Cutaneous reactions range from morbilliform rashes to potentially fatal Stevens-Johnson syndrome, toxic epidermal necrolysis or DRESS (drug rash with eosinophilia and systemic symptoms) with carbamazepine, phenytoin or barbiturate

therapy.[6,7,135] Cutaneous reactions typically occur early in therapy.[6,7,135] Patients who experienced an idiosyncratic dermatologic reaction should avoid the implicated agent and any structurally similar agents.[6,7,135] Patients of Chinese or East South Asian descent should receive genetic testing. Those testing positive for the HLA-B*1502 allele are at significantly increased risk of potentially fatal reactions and should avoid these medications.[6,7,135]

Long-term adverse events include gingival hyperplasia and hirsutism with phenytoin, shoulder-hand syndrome and Dupuytren's contractions with barbiturates and weight gain with valproic acid[6,7,135] Hepatic microsomal induction by phenytoin, phenobarbital, carbamazepine and primidone is associated with lipid abnormalities, while impaired calcium absorption, increased vitamin D catabolism, and increased parathyroid function result in increased bone turnover and loss. Osteoporosis and fractures may occur especially in patients at increased risk of a fall.[6,7,135] Two large meta-analyses have evaluated this risk:

Shen et al, performed a meta-analysis of 22 studies evaluating fracture risk in patients receiving antiepileptic drug therapy.[137]The use of any antiepileptic drug was associated with an increase of fracture (Relative Risk 1.86; 95% CI, 1.62-2.12). The difference maintained significance for both enzyme-inducing and non-enzyme-inducing antiepileptic drugs. Enzyme-inducing antiepileptic drugs were associated with a greater risk than the non-inducing antiepileptic drugs (RR 1.18; 95% CI 1.11-1.25). Combination therapy was associated with a greater risk than monotherapy (RR = 1.61; 95% CI 1.40–1.87). Fracture risk increased significantly with phenobarbiturate 78% (RR 1.78, 95% CI 1.64-1.93), topiramate 39% (RR 1.39; 95% CI 1.02-1.90) and phenytoin 70% (RR 1.70; 95% CI 1.26-2.29).

Fraser et al, performed a meta-analysis evaluating enzyme-inducing antiepileptic drugs and fracture risk in people with epilepsy.[138] Thirteen studies (2 appearing in Shen et al) evaluated 68,973 adults. Studies results were divided with respect to the influence of enzyme-inducing antiepileptic drugs on either fracture risk and reduced bone mineral density. The largest study (N=63,239) was the most methodologically rigorous and demonstrated an increased hazard ratio (HR) for both any fracture (9-22%) or hip fracture (49-53%) with the use of an enzyme-inducing antiepileptic drugs.

Teratogenic adverse events are 2-3 times more common in mothers receiving antiepileptic drug therapy than in the general population (2-6% vs 1-2% respectively).[6,7,135] The risk is highest with valproate. It appears valproate teratogenic effects are dose related; valproate regimens of <700 mg daily resulted in a 5.6% rate of malformations, while the rate increases to 24.2% when valproate dosages exceeded 1500 mg/day.[135]

Sudden Unexpected Death in Epilepsy Patients (SUDEP) Sudden unexpected death in epilepsy appears to be seizure related.[21,139,140] Additional risk factors include long-standing epilepsy and tonic-clonic seizures. Most commonly death is unwitnessed and occurs at night, when in the prone position. It is estimated to cause 7,000 deaths per year in Europe and the US and is second only to stroke in the number of deaths. The incidence is estimated at 1.16 deaths per 1000 epilepsy patients with young people up to 24 times more likely to die from sudden death than the general population. The risk of SUDEP is 7% in the general epilepsy population and 12% in patients who are untreated or uncontrolled (refractory, not in remission). No correlation between antiepileptic medication and SUDEP has been identified. Seizure reduction is the only strategy currently known to mitigate the risk as SUDEP is not well understood.

Suicide Since 2009, the FDA has required manufacturers of antiepileptic drugs to provide information about the increased risk of suicidal thoughts and behavior associated with treatment. [141,142] This resulted from an FDA review of 11 epilepsy mediations in 199 clinical trials which found antiepileptic medication usage associated with a two-fold increase in the risk of suicidal behavior or thoughts compared to patients receiving placebo. The finding was consistent among all 11 agents. Risk was noted within 1 week and extended throughout the entire 24 weeks of evaluated data. The risk of suicide was higher when these medications were prescribed for epilepsy compared to other uses. Although only 11 medications were included in the analysis it is believed the risk extends to any antiepileptic medication. Professionals involved in the care of patients

should monitor patients for changes in behavior, depression or suicidal thoughts. If present, the contribution of the antiepileptic medication or underlying illness should be considered.

Phenytoin[6,109,134,136] High phenytoin concentrations are associated with nystagmus, decreased level of consciousness, sedation, lethargy, ataxia, confusion, coma, seizures, and apnea. Dystonias and movement disorders may result from dopaminergic and serotonergic activity. Symptoms of chronic toxicity include peripheral neuropathy, cerebellar degeneration and ataxia. Cardiovascular toxicity may occur with rapid intravenous administration. Infusion rates below 50 mg/min are recommended. Toxicity manifests with bradycardia, conduction delays (PR and QRS interval prolongation), AV block, ventricular arrhythmias, fibrillation or asystole. Patients at increased risk are older, have cardiovascular disease or are critically ill. Intramuscular administration is best avoided due to the risk of necrosis, sterile abscess, myonecrosis and erratic absorption. Gangrene has been reported rarely.

Carbamazepine[6,109,134,136]: Therapy may be associated with hyponatremia, rash, transient leukopenia, thrombocytopenia and rarely agranulocytosis or aplastic anemia during the first month of therapy. The anticholinergic properties of carbamazepine delay gastrointestinal transit and may lead to erratic absorption. Mild elevations in liver function tests occur in 10% of patients receiving chronic therapy. Although rare, cardiac conduction delays and seizures may result from high plasma levels as well as CNS depression, ataxia, nystagmus, hyponatremia, hyperglycemia and elevated liver enzymes.

Valproate[6,109,134,136] therapy may cause reversible thrombocytopenia (27%), leukopenia, neutropenia, erythroblastopenia and pancreatitis. Chronic valproate therapy has been associated with elevated ammonia levels in the absence of hepatic failure. Conversely, elevated ammonia, lactate and aminotransferase levels may suggest hepatotoxicity which can be either intrinsic (benign) or idiosyncratic (potentially fatal). Severe hepatotoxicity is most common in children <2 years of age and in patients receiving concomitant enzyme-inducing drugs. Patients with higher serum levels may exhibit drowsiness, hypotension, respiratory depression or electrolyte abnormalities with anion gap metabolic acidosis.

Antiepileptic adverse effects are best minimized with monotherapy when possible; with individualized drug dosing; with slow uptitration to maintenance dosing; with consideration of patient's comorbidities, concomitant medications and potential for drug interactions. Therapeutic drug monitoring may improve safety in specific settings (e.g. multiple antiepileptic drugs, pregnancy).[2,5,28,96,143-145]

Table 9: Adverse Events

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
			Barbiturates			Hydantoins		Succinimides		
CARDIOVASCULAR										
Bradycardia			X	X						X
Chest Pain						X				X
Congestive heart Failure		X								
Hyperemia									X	
Hypertension		X								X
Hypotension		X	X	X						
Palpitation										X
Syncope		X	X	X						
Tachycardia										X
Thrombophlebitis		X								
Ventricular Conduction Depression							X			
Ventricular Fibrillation							X			
CENTRAL NERVOUS SYSTEM										
Abnormal Dreams										X
Agitation			X	X						
Aggressiveness								X	X	
Amnesia										5-21%
Anxiety			X	X				X	X	X
Asthenia										10-27%
Ataxia	X			X	X			X	X	
Auditory Hallucinations									X	
CNS Depression (e.g. drowsiness, sedation, somnolence)				X		X	X	X	X	
Cognitive Dysfunction/Impairment								X	X	
Confusion	X		X	X			X		X	X
Convulsions	X									

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Decreased Coordination							X			X
Dizziness/Vertigo	X	X	X	X	X	X	X	X	X	4-25%
Depression	X	X	X						X	4-5%
Dyskinesia					X		X			
Emotional disturbance, lability					X					X
Euphoria								X		
Excitement	X									
Fatigue	X	X				X		X		
Gait Disturbance										X
Hallucination/Delirium		X	X	X						X
Headache	X	X	X	X		X	X	X	X	31%
hiccups								X	X	
Hostility										X
Hyperirritability					X					
Hyperkinesia			X	X				X		
Insomnia			X	X		X	X		X	9-15%
Instability								X	X	
irritability									X	
Lethargy								X		
Motor Twitching							X			
Nervousness			X	X			X		X	7-11%
Nightmare/Night Terrors			X	X				X		
Nystagmus					X	X	X			1-8%
Paresthesia	X	X								X
Peripheral Neuritis		X								
Personality Disorder										X
Photophobia/Photosensitivity	X	X							X	X
Psychiatric disturbance			X	X				X		
Psychosis									X	X

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Seizure Exacerbation		X					X			
Sleep disturbance								X		
Speech Disorder		X								
Somnolence	X		X	X						
Thinking Disorder			X	X						6%
Slurred Speech							X			
Somnolence										19-30%
Speech Disturbance										X[£]
Suicidal behavior/intentions								X	X	
Tremor										19-57%
CONNECTIVE TISSUE SYSTEM										
Coarsening of facial features							X			
Enlarged lips							X			
Gingival hyperplasia							X			
Hypertrichosis							X			
Peyronie's disease							X			
DERMATOLOGIC										
Alopecia		X								6-24%
Bullous, Exfoliative, Purpuric Dermatitis							X			
Dry Skin										X
Exfoliative Dermatitis		X	X	X						
Hirsutism		X[¥]						X		
Injection Site Reactions				X						
Lupus Erythematosus								X		
Purpuric Rash		X								
Skin discoloration		X								
Skin Eruptions					X					
Stevens-Johnson Syndrome	X		X	X		X	X	X	X	X
Toxic Epidermal Necrolysis	X	X		X			X			X

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Pruritus/Rash/Urticaria/erythematous	X	X	X			X		X	X	6%
Scarlantiform rashes							X			
ENDOCRINE/METABOLIC										
Acidosis, metabolic acidosis	X									
Diabetic Ketoacidosis										3-8%
Electrolyte disturbances	X									
Hyperglycemia	X									X
Weight Gain										4-9%
Weight Loss								X	X	6%
GASTROINTESTINAL										
Abdominal pain		X						X	X	9-23%
Anorexia	X	X						X	X	4-12%
Constipation		X	X	X	X		X		X	X
Cramps								X		
Diarrhea	X	X				X		X	X	13-23%
Epigastric Pain								X	X	
Eructation/Flatulence										X
Fecal Incontinence										X‡
Gastric Upset								X		8-11%
Gastroenteritis										X‡
Glossitis		X								X‡
Hematemesis										X
Increased Appetite										X
Nausea	X	X	X	X	X	X	X	X	X	15-48%
Pancreatitis										X
Stomatitis		X								
Taste perversion	X						3.3			X
Vomiting	X	X	X	X	X	X	X	X	X	15-27%
GENITOURINARY										

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Albuminuria		X								
Amenorrhea										X
Breast Enlargement										X
Cystitis										X
Decreased libido										X[£]
Dysmenorrhea										X
Glycosuria	X									
Increased Libido								X		
Metorrhagia										X[£]
Microscopic Hematuria								X	X	
Oliguria		X								
Polyuria	X									
Proteinuria									X	
Sexual Disorder/Dysfunction		X			X					
Urinary Frequency/Hesitancy		X								X
Urinary incontinence										X
Urinary Retention		X								
Urinary Tract Infection										X
Vaginal Bleeding								X		
Vaginitis										X
HEMATOLOPOIETIC										
Agranulocytosis	X	X			X		X	X		X
Aplastic Anemia	X	X								X
Ecchymosis										4-5%
Eosinophilia		X						X	X	
Granulocytosis					X		X			
Leukocytosis		X								
Leukopenia	X	X					X	X	X	
Lymphadenopathy		X				X	X			

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Macrocytosis anemia							X			
Megaloblastic anemia			X	X	X		X			
Monocytosis									X	
Pancytopenia ± bone marrow suppression		X					X	X	X	
Red cell hypoplasia/aplasia					X					
Thrombocytopenia	X	X					X			1-24%
HEPATIC										
Hepatitis		X								
Hepatic necrosis	X									
Jaundice	X									
Liver Damage/Failure		X	X	X			X			
Liver Enzyme Abnormalities	X	X								X
IMMUNOLOGIC										
Immunoglobulin abnormalities							X			
Periarteritis Nodosa							X			
Systemic Lupus Erythematosus						X	X			
Toxic Hepatitis							X			
Accidental injury										X
Allergic Reaction										X
Anaphylactoid/anaphylaxis reaction	X									X
OTHER										
Angle-closure glaucoma	X									
Chills		X								X‡
Conjunctivitis		X								X‡
Deafness										X
Ear Infection										X
Edema		X								
Fever	X	X		X		X	X			6%
Flu-like symptoms										12%

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Gum hypertrophy						X		X		
Hypothermia										X
Hypersensitivity			X	X			X			
Tinnitus	X	X								1-7%
Viral Infection										X
Malaise										X
Neck Pain										X‡
Neck Rigidity										X‡
Periorbital Edema									X	
Sensory peripheral polyneuropathy							X			
Sulfonamide cross-sensitivity	X									
Tongue Swelling								X		
Visual Disturbances (double, blurred vision)	X	X			X	X		X	X	12-16%
MUSCULOSKELETAL										
Arthralgia										X
Arthrosis										X‡
Back Pain										X
Flaccid paralysis	X									
Myalgia										X
Myasthenia										X
RESPIRATORY										
Apnea			X	X						
Cough										X
Dyspnea		X								1-5%
Epistaxis										X
Hypoventilation			X	X						
Laryngospasm			X							
Pharyngitis										2-8%
Pneumonia		X								X

Adverse Events	Acetazolamide	Carbamazepine	Pentobarbital	Phenobarbital	Primidone	Ethotoin	Phenytoin	Ethosuximide	Methsuximide	Valproic Acid Derivatives
Respiratory Depression			X	X						
Respiratory Tract Irritation										12-20%
Rhinitis										5%
Sinusitis										X

Key: X=frequency is unreported or ≤10%; ¥ = extended release capsule only; £ = extended release tablet only; ǂ = delayed-release tablets only

Drug Interactions:

Drug interactions are common in patients receiving treatment for epilepsy or epilepsy syndromes. Approximately 20% of patients do not achieve an adequate clinical response with monotherapy requiring multiple medications to achieve seizure remission.[144] Epilepsy demonstrates a bimodal age distribution placing the elderly at greater risk. The elderly have more comorbidities than younger patients, receive cumbersome medication regimens with the potential for drug interactions and the addition of antiepileptic medications further compounds this risk.[11,146] The major mechanism of drug interaction between combinations of antiepileptic drugs or other medications involves an interaction with hepatic microsomal metabolism.[6,7,17,88,134,143,144,147,145] Broad-spectrum cytochrome P450 (CYP) enzyme induction occurs with carbamazepine, pentobarbital, phenytoin, phenobarbital, and primidone affecting CYP1A2, 2C9, 2C19, 3A4, glucuronyl transferases (UGT) and epoxide hydrolases. Aside from interfering with the metabolism of other medications, the antiepileptic medications are themselves metabolized as substrates by hepatic microsomal metabolism. As enzyme inducers and substrates, increased clearance may be noted with phenobarbital, phenytoin, carbamazepine and primidone.[148] Carbamazepine and ethosuximide are metabolized via CYP3A4 isoenzymes. Phenobarbital, pentobarbital and phenytoin are metabolized by CYP2C9 and 2C19 isoenzymes while valproate is primarily metabolized by glucuronidation with some CYP2C19 metabolism. See **Table 10** for a summary of the antiepileptic drugs interaction with hepatic microsomal enzyme functioning. The hepatic microsomal enzyme interactions between antiepileptic medications are presented in **Table 11.**

Table 10: Hepatic Enzyme Drug Interaction Table [6,7,17,88,134,143,144,147]

	Substrate	Inhibitor	Inducer
Acetazolamide	None	None	None
BARBITURATES Phenobarbital Pentobarbital Primidone	None	None	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5, 3A6, 3A7
Carbamazepine	CYP3A4	None	CYP 1A2, 3A4
HYDANTOINS Phenytoin Ethotoin	CYP2C9, CYP2C19	None	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5, 3A6, 3A7
SUCCINIMIDES Ethosuximide Methsuximide	CYP3A4	None	CYP 3A4 for methsuximide
Valproic Acid derivatives	CYP2C19	CYP2C9, 2D6, 3A4	None

Table 11: Drug Interactions Between Antiepileptic Drugs[6,7,88,134,143-145,147]

Baseline AED	Added Antiepileptic Drug	Effect
Carbamazepine	Felbamate, valproic acid	Increase carbamazepine epoxide level
	Acetazolamide, vigabatrin	Increase carbamazepine levels
	Felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide (in pediatrics)	Decrease carbamazepine levels
Ethosuximide	Valproic acid	Increase ethosuximide levels

Baseline AED	Added Antiepileptic Drug	Effect
	Carbamazepine, phenobarbital, phenytoin, primidone	Decrease ethosuximide levels
Phenobarbital	Acetazolamide, felbamate, oxcarbazepine, phenytoin, rufinamide (in pediatrics), valproic acid	Increase phenobarbital levels
	Vigabatrin	Decrease phenobarbital levels
Phenytoin	Clobazam, felbamate, methsuximide, oxcarbazepine, phenobarbital, rufinamide (in pediatrics), topiramate	Increase phenytoin levels
	Carbamazepine, valproic acid, vigabatrin	Increase phenytoin levels (valproic acid increases total levels while free levels remain unchanged or slightly increased)
	Acetazolamide	Increase osteomalacia and rickets risk
Primidone	Valproic acid	Increase phenobarbital and primidone levels
	Carbamazepine, phenytoin	Decrease primidone and increase phenobarbital levels
	Acetazolamide	Increase osteomalacia and rickets risk
Valproic acid derivatives	Felbamate	Increase valproic acid levels
	Carbamazepine, ethosuximide, lamotrigine, phenobarbital, primidone, phenytoin, topiramate	Decrease valproic acid levels
	Felbamate	Increase valproic acid levels

Drug interactions are additionally common between antiepileptic drugs and other medications. A summary of more significant interactions is presented in **Table 12**. Of particular interest in women of child-bearing potential, antiepileptic drugs may cause hormonal contraceptive failures. Induction of CYP450 enzymes and increased glucuronidation may lead to reduced serum concentrations of estrogen and/or progesterone. The use of non-enzyme inducing antiepileptic drugs is preferred, when possible.[48] Females receiving an antiepileptic drug which induces CYP450 enzymes may require alternative contraception methods, including depot-medroxyprogesterone acetate (administered more frequently), levonorgestrel, copper IUD, barrier methods or oral contraceptives containing >50 mcg ethinyl estradiol. Due to the prolonged effect of the antiepileptic drugs on enzyme induction, enhanced contraception should continue for 4 weeks following discontinuation.[149,150]

Table 12: Drug Interactions Between AEDs and Other Medications [6,7,88,134,143,144,147]

Baseline AED	Interacting Medication	Effect
Acetazolamide	Methenamine, sulfonamides	Crystalluria
	Sotalol, droperidol	Cardiotoxicity, QT prolongation
	Mecamylamine	Increase mecamylamine toxicity
	Amphetamine	Increased amphetamine levels
	Quinidine	Increase quinidine levels
	Digitalis	Increase digitalis levels
	Metformin	Increase risk for lactic acidosis
	Flecainide	Increase flecainide levels
	Memantine	Increase memantine levels
	Lithium	Decrease lithium levels

	Salicylates	Increase adverse/toxic effects of each
Carbamazepine	Cimetidine, erythromycin, fluoxetine, isoniazid	Increase carbamazepine level
	Doxycycline	Decrease doxycycline efficacy
	Theophylline	Decrease theophylline efficacy
	Warfarin	Decrease warfarin efficacy
	Nefazodone	Decrease nefazodone and increase carbamazepine level
	Hormonal contraceptives	Decrease contraceptive efficacy
Phenobarbital	Acetazolamide	Increase phenobarbital levels
	Hormonal contraceptives	Decrease contraceptive efficacy
Phenytoin	Amiodarone, cimetidine, chloramphenicol, disulfiram, ethanol (acute), fluconazole, fluoxetine, isoniazid	Increase phenytoin levels
	Antacids, ethanol (chronic)	Decrease phenytoin levels
	Warfarin	Increase or decrease INR
	Hormonal contraceptives	Decrease contraceptive efficacy
	Folic acid	Decrease folic acid levels
	Quinidine	Decrease quinidine levels
	Vitamin D	Decrease vitamin D levels
Primidone	Isoniazid, nicotinamide	Decrease primidone metabolism
	Chlorpromazine	Decrease chlorpromazine levels
	Corticosteroids	Decrease corticosteroid levels
	Quinidine	Decrease quinidine levels
	Tricyclic antidepressants	Decrease tricyclic antidepressant levels
	Furosemide	Reduced renal sensitivity
Valproic acid derivatives	Cimetidine	Increase valproic acid levels
	Salicylates	Increase free valproic acid levels

Key: AED=antiepileptic drug

Summary:

Antiepileptic drug therapy has advanced over the last century. Overall the older anticonvulsant agents are associated with higher rates of adverse and serious adverse events, although newer agents have not surpassed them in efficacy. Clinical practice guidelines continue to prefer ethosuximide and valproic acid in absence seizures; generalized-onset seizure treatment considers valproate, phenobarbital and carbamazepine among the first-line agents; Valproic acid remains appropriate for Lennox Gastaut syndrome and myoclonic seizures; Status epilepticus treatment (after first-line benzodiazepines), includes barbiturates and phenytoin; and for partial-onset seizures, carbamazepine, valproate and phenytoin are among the first-line agents. Among the older antiepileptic medications, the enzyme inducing agents, carbamazepine, phenytoin, phenobarbital and primidone are associated with greater frequency and severity of adverse events than other older or newer agents.

In the treatment of epilepsy, ethosuximide provides similar efficacy with a superior safety profile than valproic acid including a reduction in long-term development of tonic-clonic seizures. In the treatment of generalized and partial-onset seizures no significant difference in efficacy was found in comparisons of phenytoin and valproic acid, phenytoin and carbamazepine, carbamazepine and valproic acid. In neonatal seizures, phenytoin and phenobarbital performed

similarly. In the treatment of refractory epilepsy, acetazolamide and methsuximide demonstrated low, typically short-lived, clinically pertinent rates of efficacy. In status epilepticus, valproic acid may be preferred to phenytoin or phenobarbital as it demonstrated equivalent acute efficacy, higher tolerability and lower rates of recurring seizures over 24-hr.

Although labeled for use in bipolar disease, evidence is controversial for valproic acid. Use of valproate extended-release may be preferred to theoretically reduce adverse events and improve adherence over valproate delayed-release formulations in which a mg-for-mg conversion may yield therapeutic levels in 95% of patients. Carbamazepine use in bipolar disorder may be limited by adverse events including cardiac conduction delays and rash. Finally, Valproic acid derivatives appear efficacious in the prophylaxis of migraine headache.

Methsuximide was not distinctly recommended in any clinical practice guideline. Other agents appear to have a defined place in therapy even after weighing the higher risk of adverse events, and drug interactions with these agents versus other, mostly newer, antiepileptic medications.

Appendix I: Evidence

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Epilepsy					
Cochrane Reviews					

Nolan et al[115] 2016
 	
Cochrane Review (5 RCTs)
 	
Data on 699 patients in 5 additional trials not included as individual patient data was unavailable
	N=699	Monotherapy of partial and generalized epilepsy (excluding myoclonus and absence seizures), assessing individual participant data
		
		Follow-up at 1-91 months of therapy
			Valproate
			Phenytoin
				<u>Retention Time</u>
				• Stratified by seizure type
				  ○ Non-statistically favored valproate (Harms Ratio [HR] 1.09; 0.76-1.55).
				• Generalized seizures
				  ○ Non-statistically favored phenytoin (HR of 0.98; CI 0.59-1.64)
				• Partial onset seizures
				  ○ Non-statistically favored valproate (HR 1.20; 0.74-1.95)
				
				<u>Time to 12-month Remission Free Period</u>
				• Stratified by seizure type
				  ○ Non-statistically favored valproate (HR 0.98; 0.78-1.23)
				• Generalized seizures
				  ○ Non-statistically favored phenytoin (HR 1.04; 0.77-1.40)
				• Partial onset seizures
				  ○ Non-statistically favored valproate (HR 0.90; 0.63-1.29)
				
				<u>Time to Achieve a 6-month Seizure Free Period</u>
				• Stratified by seizure type
				  ○ Non-statistically favored valproate (HR 0.95; 0.78-1.15)
				• Generalized seizures
				  ○ Non-statistically favored valproate (HR 0.92; 0.72-1.18)
				• Partial onset seizures
					Not Reported

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				○ Non-statistically favored valproate (HR 0.99; 0.73-1.35) <u>Time to First, Post-Randomization Seizure</u> • Stratified by seizure type ○ Non-statistically favored valproate (0.93; 0.75-1.14) • Generalized seizures ○ Non-statistically favored valproate (HR 1.03; 0.77-1.39) • Partial onset seizures Non-statistically favoring phenytoin (HR 0.83; 0.62-1.11).	
Nolan et al[117] 2015 Cochrane Review (4 RCTs) Data from 8 additional trials (N=597) not included due to lack of individual participant data	N=595	Monotherapy of partial onset seizures (simple partial, complex partial, generalized tonic-clonic) or generalized seizures assessing individual participant data *Up to 30% of participants may have had their seizure type misclassified	Phenytoin Carbamazepine	<u>Time to Treatment Withdrawal (Harms Ratio (HR); 95% confidence interval)</u> • Stratified by Epilepsy Type ○ Non-statistically favored carbamazepine (HR 1.04; 0.78-1.39) • Generalized Epilepsy ○ Non-statistically favored phenytoin (HR 0.42; 0.18-0.96) • Partial Epilepsy ○ Non-statistically favored carbamazepine (HR 1.18; 0.87-1.60) <u>Time to 12-month Remission</u> • Stratified by Epilepsy Type ○ Non-statistically favored phenytoin (HR 1.01; 0.78-1.31) • Generalized Epilepsy ○ Non-statistically favored phenytoin (HR 1.17; 0.53- 2.57) • Partial Epilepsy ○ Non-statistically favored phenytoin (HR 0.94; 0.71-1.25) <u>Time to 6-month Remission</u> • Stratified by Epilepsy Type	<u>Withdrawal Due to Adverse Events</u> • Carbamazepine 9% vs Phenytoin 4% (Risk ratio (RR) 1.42; 1.13-1.80; *p*=0.014) <u>Most commonly reported for phenytoin and carbamazepine (from narrative data)</u> <u>Gastrointestinal:</u> abdominal pain, nausea, vomiting <u>Central nervous system</u>: drowsiness, tiredness, fatigue, sedation <u>Dermatologic</u>: rash <u>Endocrine</u>: decreased libido, impotence or both <u>Neuromuscular:</u> motor disturbances: ataxia, incoordination, nystagmus,

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				○ Non-statistically favored phenytoin (HR 1.11; 0.81-1.37) • Generalized Epilepsy ○ Non-statistically favored phenytoin (HR 1.30; 0.89-1.92) • Partial Epilepsy ○ Non-statistically favored phenytoin (HR 1.02; 0.79-1.33) Time to First Seizure Post-Randomization • Stratified by Epilepsy type ○ Non-statistically favored phenytoin (HR 0.85; 0.70-1.04) • Generalized Epilepsy ○ Non-statistically favored phenytoin (HR 0.84; 0.57-1.24) • Partial Epilepsy Non-statistically favored phenytoin (HR 0.86; 0.68-1.08)	tremor, slowing mental function, inattention, psychomotor retardation Dysmorphic and idiosyncratic: hypertrophy, hirsutism; acne skin problems Cognitive effects: depression, memory problems Reported only with carbamazepine: headache
Nolan et al[118] 2013 Cochrane Review (4 RCTs) Data from 4 additional trials (N=352) not included due to lack of individual participant data	N=599	Monotherapy with phenobarbitone vs phenytoin for partial-onset and generalized, tonic-clonic seizures in adults and children assessing individual participant data	Phenobarbitone Phenytoin	Time to Treatment Withdrawal (Harms Ratio (HR); 95% confidence interval) • All Participants – favors phenytoin ○ (HR 1.62; 1.23-2.14; *p*=0.0006) ○ Results consistent when assessed by random effects model and when adult information was evaluated separately from children ○ Phenytoin less likely to be withdrawn than phenobarbitone • Pooled Data (adjusted for seizure type and fixed effects) ○ Statistically favors phenytoin (HR=1.62 1.23-2.14; *p*=0.0007) by random effects mod • Generalized Epilepsy ○ Significantly favors phenytoin (HR 4.04; 1.61-10.14; *p*=0.003) by random effects model	

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				• Partial Epilepsy ○ Significantly favors phenytoin (HR 1.48; 1.10-1.98; *p*=0.009) by random effects model <u>Time to 12-month Remission</u> • All Participants ○ Non-statistically favors phenytoin ○ (HR 0.90; 0.69-1.19; *p*=0.44) • Generalized Epilepsy ○ Non-statistically favors phenytoin ○ (HR 0.77; 0.46-1.28; *p*=0.31) • Partial Epilepsy ○ Non-statistically favors phenytoin (HR 0.96; 0.70-1.33, *p*=0.82) <u>Time to 6-month Remission</u> • All Participants ○ Non-statistically favors phenytoin (HR 0.90; 0.71-1.14; *p*=0.38) • Generalized Epilepsy ○ Non-statistically favors phenytoin (HR 0.79; 0.51-1.24, *p*=0.31) • Partial Epilepsy ○ Non-statistically favors phenytoin (HR 0.94; 0.71-1.25; *p*=0.69) <u>Time to First Seizure Post-Randomization</u> • All Participants ○ Non-statistically favors phenobarbitone (HR 0.86; 0.69-1.08; *p*=0.19) • Generalized Epilepsy ○ Non-statistically favors phenytoin (HR 1.14; 0.73-1.78; *p*=0.56) • Partial Epilepsy Non-statistically favors phenobarbitone (HR 0.78; 0.61-1.01; *p*=0.06)	

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects

Posner et al[114] 2005
 	
Cochrane Review (5 Trials)
 	
Evidence not pooled
• Poor methodology
• Lack of power
	N=160	Children and adolescents with absence seizures	Ethosuximide
			Sodium Valproate
			Lamotrigine
				<u>Study 1: Lamotrigine vs Placebo</u>
				• Lamotrigine better than placebo in maintaining seizure freedom
				
				<u>Study 2,3,4: Ethosuximide vs Valproate</u>
				• Seizure Freedom – No difference
				• Achieve at least 50% reduction in seizure frequency – No difference
				• Achieve at least 80% difference in seizure frequency – No difference
				
				<u>Study 5: Valproate vs Lamotrigine</u>
				• Seizure freedom at 12-months – No difference
				• Seizure free status at 1 month
				  ○ Valproate 52.6% vs Lamotrigine 5.3% (*p*=0.004)
				• Seizure free status at 3 months
				  ○ Valproate 63.1% vs Lamotrigine 36.8% (*p*=0.19)
				• Seizure free status at 12 months
				• Valproate 68.4% vs Lamotrigine 52.6% (*p*=0.51)
					• Not Reported

Systematic Reviews/Meta-Analysis					
Brigo et al[126] 2013 Systematic Review/meta-analysis (3 Trials) Included RCTs comparing	N=287	Generalized, convulsive status epilepticus Two trials of IV-VPA vs IV-PHT One trial of IV-PB vs IV-PHT	Intravenous Phenytoin (IV-PHT) 18 mg/kg IV in saline at 50 mg/min or over 20 min Intravenous Phenobarbital (IV-PB) 15 mg/kg at 100 mg/min MAX	<u>Clinical seizure cessation</u> • IV-VPA vs IV-PHT (OR 1.81; 0.60-5.52) non-significantly favors IV-VPA • IV-PB vs IV-PHT (OR 1.81; 1.02-3.20) non-significantly favors IV-PB <u>Indirect Comparison of IV-VPA vs IV-PB</u> • IV-VPA = IV PB (OR 1.00; 0.36-2.76) non-significant	<u>Adverse Events</u> <u>IV-VPA < IV-PHT</u> (OR 0.22; 0.06-0.87) non-significant Study 1: • IV-VPA: respiratory depression (1/35), liver dysfunction (3/35) • IV-PHT: Hypotension (2/33), respiratory depression (2/33), liver

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Intravenous valproate, phenobarbital and phenytoin			Intravenous Valproate (IV-VPA) 30 mg/kg IV in saline over 15-20 minutes		dysfunction (2/33) Study 2: • IV-VPA: no adverse events • IV-PHT: cardiac arrhythmia (1/9), hyponatremia (1/9) <u>IV-PB > IV-PHT</u> (OR 1.32; 0.75-2.34) non-significant • IV-PB: hypoventilation (12/91), hypotension (31/91), cardiac arrhythmias (3/91) • IV-PHT: hypoventilation (10/101); hypotension (27/101), cardiac arrhythmia (7/101) <u>Indirect Comparison of IV-VPA vs IV-PB</u> • IV-VPA > IV-PB (OR 0.17; 0.04-0.71) non-significant

Marson et al[120]
 	
2002
 	
Meta-analysis (5 Trials)
 	
Randomized, monotherapy trials
	N=1265	Monotherapy treatment of partial-onset or generalized-onset seizures
		
		Included new, relapse and inadequately treated children and adults
			Carbamazepine (CBZ)
			
			Valproate (VPA)
				<u>Retention Time (HR=1=advantage CBZ)</u>
				• Overall, adjusted for seizure type
				  ○ HR 0.97 (95% CI, 0.79-1.18)
				• Generalized seizures
				  ○ HR 0.89 (0.61-1.29)
				• Partial seizures
				  ○ HR 1.00 (0.79-1.26)
				
				<u>Time to 12-Month Remission</u>
				• Overall, adjusted for seizure type
				  ○ HR 0.87 (0.74-1.02)
				• Generalized seizures
				  ○ HR 0.96 (0.75-1.24)
					Not Reported

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects

				• Partial Seizures
				  ○ HR 0.82 (0.67-1.00)
				  ▪ Test for interaction between treatment and seizure type found no significant interaction. Interpret this significant finding cautiously
				
				<u>Time to First Seizure, Post-Randomization</u>
				
				• Overall, adjusted for seizure type
				  ○ HR 1.09 (0.96-1.25)
				• Generalized seizures
				  ○ HR 0.86 (0.68-1.09)
				• Partial seizures
				  ○ HR 1.22 (1.04-1.44)
				  ▪ A significant advantage for CBZ was supported with a significant interaction between treatment and seizure type (χ^2 (1)=5.73; *p*=0.017)	

Other Trials, Studies, Reports					
Shinnar et al[113] 2015 Open-label, long-term followup cohort of Glauser[111,112] trial participants	N=446	Long-term followup of childhood absence epilepsy for development of generalized, tonic-clonic seizures	Ethosuximide Valproate Lamotrigine	Medial followup: 7.0 years Percentage of patients developing a generalized, tonic-clonic seizure (GTC): 12% (IQR 2.3%-6.3%) • 28% no longer receiving anticonvulsant therapy Post-randomization median time to GTC: 4.7 years Age at first GTC post-randomization: 13.1 <u>Univariate Analysis</u> <u>Five-Year Risk of Developing a GTC Seizure</u>	Not Reported

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				Age at enrollment • ≥9 years 19%; (95% CI, 12%-28%; *p*=0.0009) • 7-8 years 6%; (3%-13%; *p*=0.03) • ≤6 years 3.9%; (1.7%-8.5%; *p*=0.0003) Baseline Electroencephalogram Results • Duration of shortest burst (*p*=0.037) Initial Treatment Assignment • Non-statistically significant Failure of Initial Treatment at 16-20 week visit (*p*<0.001) • Ethosuximide *p*<0.0001 ○ Initial responders to ethosuximide were the least likely to develop a GTC seizure • Valproate *p*=0.17 • Lamotrigine *p*=1.0 Yearly Risk of Developing a GTC Seizure: 20%	
Glauser et al[112] 2013 12-month DB, RCT	N=446	Assessment of 12-month initial monotherapy of children and adolescents with absence epilepsy Continuation of	Ethosuximide (up to 60 mg/kg/day) Valproic Acid (up to 60 mg/kg/day) Lamotrigine (up to 21 mg/kg/day	<u>Freedom from Failure Rate</u> Overall 37%; Ethosuximide 45%; Valproic Acid 44%; Lamotrigine 21% • Ethosuximide vs Valproic Acid (OR 0.94; 95% CI 0.58-1.52; *p*=0.82) • Ethosuximide vs Lamotrigine (OR 3.08; 95% CI 1.81-5.33; *p*<0.001) • Valproic Acid vs Lamotrigine (OR 2.88; 95% CI 1.68-5.02; *p*<0.001)	<u>Discontinuations due to Adverse Events</u> • Between groups, *p*<0.037 with 42% receiving valproic acid <u>Attentional Dysfunction</u> Valproic Acid vs ethosuximide or lamotrigine (*p*<0.01)

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
		Glauser, 2010[111]		Lack of Seizure Control Overall $p<0.01$ between groups 2/3 of treatment failures treated with lamotrigine	
Malamiri et al[127] 2012 RCT (Iran)	N=60	Convulsive status epilepticus or acute prolonged convulsive seizures in children ≥ 2 years of age with seizure uncontrolled 5 min after an IV bolus diazepam (0.2 mg/kg)	Valproate 20 mg/kg infusion over 5-10 min Phenobarbital 20 mg/kg infusion at a max rate of 100 mg/min	Seizure Termination • Valproate 90% vs Phenobarbital 77%; p=0.189 Seizure Recurrence within 24 hours Valproate (4/23 patients) vs Phenobarbital (12/23); $p=0.07$	Adverse Events: Lethargy, vomiting, hypotension, respiratory depression Valproate < Phenobarbital; $p<0.001$
Rai et al[116] 2011 RCT India	N=100	Acute emergency room treatment of motor focal or generalized tonic-clonic seizures in children age 3-12	If seizing at presentation received 0.3 mg/kg diazepam in addition to IV loading doses (20 mg/kg) followed by maintenance doses • IV-Valproate • IV-Phenytoin	Control of Seizures for 24 Hours • Valproate 93% vs Phenytoin 97% ($p=0.345$) Time to Cessation of Presenting Seizures -Requiring diazepam (minutes) • Valproate 25.44 ± 10.34 vs Phenytoin 24.76 ± 12.60 ($p=0.90$) Percentage with Drug Levels in Therapeutic Range at 4 hr and 24 hours • Not different ($p>0.05$) Time to Regain Consciousness (minutes) Valproate 58.33 ± 28.50 vs Phenytoin 135 ± 62.10 ($p=0.010$)	Changes in Cardiorespiratory Parameters (HR, RR, BP, O_2 Saturation) No differences ($p>0.05$)
Glauser et al[111] 2010 16-week DB, RCT	N=453	Initial monotherapy of children and adolescents with absence	Ethosuximide (up to 60 mg/kg/day) Valproic Acid (up to 60 mg/kg/day)	Medication Dosed at Maximal Dose • Lamotrigine 58.9% • Ethosuximide 17.5% • Valproic Acid 20.5% Freedom from Failure Rate	Discontinuation Rate due to Adverse Events • No difference between groups

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
		epilepsy	Lamotrigine (up to 21 mg/kg/day Analysis via intent-to-treat analysis.	Overall 47%; Ethosuximide 53%; Valproic Acid 58%; Lamotrigine 29% • Ethosuximide vs Valproic Acid (p=0.35) • Lamotrigine vs Ethosuximide p<0.001 • Lamotrigine vs Valproic Acid p<0.001	Attentional Dysfunction • Valproic Acid (49%) • Ethosuximide (33%) (odds ratio 1.95; 95% CI 1.12-3.41; p=0.03)
Katayama et al[124] 2002 PRO Japan	N=37	Children with refractory epilepsy uncontrolled with combination therapy including at least 2 of the following; carbamazepine, sodium valproate or clonazepam Age: 1-17 years (mean 8.1 years) 32 or 37 subjects with mental retardation	Acetazolamide Initial dosing with 10 mg/kg which could be increased to 20 mg/kg	Maintenance Dose • 12.2 ± 4.2 mg/kg Steady State Serum Level • 6.2 ± 4.5 mcg/mL • No correlation was found between dosage or serum level and efficacy Response • Complete remission > 3 years: 10.8% ○ Only noted in patients with localization-related (partial) epilepsies • Remission for 6 months followed by recurrence 13.5% • Reduction in seizure frequency > 50%: 16.2% • Ineffective: 59.5% Response by Medication Carbamazepine/clonazepam/acetazolamide performed superior to other combinations (p=0.05) including 2 whom maintained remission at 3 years	Adverse Events • Transient drowsiness • Kidney stone 1 patient passed as rice-grain sized stone after > 6 years of acetazolamide therapy

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Sigler et al[121] 2001 PRO, OL, UC Germany	N=112	Intractable epilepsy in children • Refractory to 1st line antiepileptic drugs Refractory to combinations of antiepileptic drugs	Methsuximide	Epilepsies Represented: Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, generalized cryptogenic, symptomatic epilepsy and West syndrome. Reduction in Seizure Frequency by ≥50% • 40/112 patients (35.7%) at mean 9.1 weeks ○ Focal epilepsy 27.5% ○ Lennox-Gastaut syndrome 39.5% ○ Full-remission 8.9% Yearly Risk Of Developing a GTC Seizure: 20%	Any Adverse Event • 41/112 (28.9%) Most Common AD (>10%) • Hiccups • Nausea/vomiting • Drowsiness Discontinuation Due to AE • 12/112 (10.7%)
Painter et al[119] 1999 RCT, SB	N=59	Neonates with seizures	Phenobarbital dosed to achieve serum levels of 25 mcg/mL Phenytoin dosed to achieve serum levels of 3 mcg/mL Failures were treated with combination phenobarbital and phenytoin	Complete Seizure Control (EEG proven) • Phenobarbital (13/30) 43% vs Phenytoin (13/29) 45% (p=1.00) • Combination therapy (p=0.67) ○ Adding phenobarbital to phenytoin, 62% ○ Adding phenytoin to phenobarbital, 57%	Adverse Events No significant changes in heart rate, heart rhythm, mean arterial pressure, respiratory status in either treatment group
Treiman et al[128] 1998 RCT, DB, MC 5 years	N=518	Overt or generalized convulsive status epilepticus in adults	• Diazepam 0.15 mg/kg → phenytoin 18 mg/kg • Lorazepam 0.4 mg/kg • Phenobarbital 15 mg/kg • Phenytoin 18 mg/kg	Percent of patients with cessation of seizure activity within 20 minutes of drug administration without recurrence within 40 minutes Length of infusion: ○ Shortest with lorazepam (p<0.001 in pairwise comparisons) ○ Longest with phenytoin regimens (p<0.001) Patients with Verified Diagnosis (N=518) • Overt status epilepticus ○ Diazepam/phenytoin 55.8%	No differences were found between groups for adverse events

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				○ Lorazepam 64.9% ○ 23 58.2% ○ Phenytoin 43.6% • Overall comparison among four groups, *p*=0.002 ○ Lorazepam was superior to phenytoin, *p*=0.002 • Subtle status epilepticus ○ No significant differences (*p*<0.18) Intent-to treat analysis (N=570) ○ No differences among treatment groups for overt status epilepticus (*p*=0.12) or for subtle status epilepticus (*p*=0.91) No 30-day outcome differences were found	
Tennison et al[122] 1991 RETRO	N=25	Children with intractable epilepsy on maximal therapy with multiple antiepileptic drugs Age: 0.8-21 years	Methsuximide added to current regimen	Epilepsies Represented: Absence, myoclonic, tonic, complex partial, secondary generalized Reduction in Seizure Frequency by ≥50% • 15/25 (60%) • Over duration of 19 months (5.2-50.7 months) only 1/15 had seizures worsen Complete Remission of Seizures: None	Not Reported
Dasheiff et al[123] 1986 OL, PRO 3 years	N=66	Patients with medically refractive complex partial seizures ± secondary generalization ± simple partial seizures (auras)	Clorazepate 15-120 mg/day Methsuximide 600-2700 mg/day Valproate 500-4000 mg daily	Seizure Frequency • Non-statistically reduced with each treatment (*p*>0.05 for each) ○ Clorazepate (6/31) ○ Methsuximide (8/39) ○ Valproate (15/57) Seizures Eliminated and Side Effects Tolerated at 6-months • Non-significant differences	Adverse Events Clorazepate: confusion, depression, intention tremor (2 patients) Methsuximide: nausea, vomiting, decreased appetite, hiccups, increased thirst, personality change, depression,

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
		who failed therapy with phenytoin, carbamazepine and/or phenobarbital	Therapy was adjunctive to a continued first-line medication	○ Clorazepate (3/31) ▪ Maintained seizure free at 12- months ○ Methsuximide (1/39) ○ Valproate (3/57)	fearfulness, irritability, nervousness, confusion, tiredness, sleepiness or headache, dizziness, unsteadiness, slurred speech adventitious movements Valproate: nausea, dysphagia, weight gain/loss, tremor, ataxia, confusion, tiredness, sleepiness, headache, elevated LFTs (1 patients and reversed with drug discontinuation)
Bipolar Disorder					
Joshi et al[132] 2010 OL, PRO 8 weeks	N=27	Bipolar I or II disorder in outpatients 6-12 years of age having severity of manic, hypomanic or mixed symptoms on the YMRS	Carbamazepine ER MAX: 1200 mg/day Median dose: 788 ± 252 mg/day	Mania Symptom Severity • Response at 2 weeks (YMRS scores) $p<0.001$ • Response at 8 weeks (YMRS scores) $p<0.001$ Mania Remission (YMRS Score < 12) at 8 weeks • 9/24 patients; 34% CGI-I measures improved or much improved • Severity of depression, 43% • Attention-deficit/hyperactivity disorder, 62% Improvement in Depression (vs baseline) • CDRS score: 34.8 ± 10.9 vs 26.9 ± 11.6; $p=0.001$ Improvement in Psychosis (vs baseline) BPRS score: 40.1 ± 9.9 vs 30.0 ± 6.8; $p<0.001$	Adverse Events: headache, gastrointestinal complaints, cold symptoms, sedation, dizziness, aches and pains, insomnia Increased body weight (0.8 ± 2.5 kg, $p=0.04$) Discontinuation Due to Adverse Events • Skin rash: 2 patients (resolved with medication discontinuation) PR and QRS Interval Prolongation • PR increase, $p<0.001$ QRS increase, $p=0.04$

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
McElroy et al[129] 2010 DB, PC, PG, RCT 8 weeks	N=60	Bipolar Spectrum Disorder (Bipolar I or II or unspecified bipolar disorder) or moderate to severe manic or hypomanic or mild manic symptoms in outpatient adults ≥ 18 years with • YMRS score 10 to <21 at baseline and 1 other study visit at least 3 days apart over the 2 weeks before baseline Receiving no psychotropic for 1 week before assessment	Divalproex ER MAX: 30 mg/kg/day	<u>Reduction in YMRS score at 8 weeks</u> • Divalproex > Placebo (p=0.024) <u>Reduction in CGI-BP</u> • Mania: Divalproex > Placebo (p=0.044) • Overall Score: Divalproex > Placebo (p=0.047) <u>Attrition Rate</u> • Overall: 53% • Divalproex ER: 43%	<u>Discontinuation Rates</u> • No difference for lack of efficacy, side effects, administrative or lost to follow-up <u>Adverse Event Rates</u> • Adverse event rates occurring in ≥ 2 patients did not differ between treatment groups
Hirschfelt et al[130] 2010 RCT 21 days	N=225	Patients with Bipolar I disorder (manic or mixed) MRS score > 25 with at least 3 items having a score of at least	Divalproex ER (individualized dosing) Mean: 2211 mg/daily Divalproex:Placebo 2:1	<u>MRS Score (mean change from baseline)</u> • Divalproex ER: -10.1 vs Placebo: -8.7 • No significant difference (p value not presented) <u>Attrition Rates</u> • Divalproex ER: 83%	<u>Serious Adverse Events Requiring Hospitalization (n=3)</u> • Edema (1): Placebo • Depression (1): Divalproex ER • Overdose (1): Divalproex ER

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
		4 on the final day of screening, washout 18-65 years		• Placebo: 82% Other Measures (non-significant) • Manic Syndrome Score • Behavior and Ideation Score • Brief Agitation Rating Scale score • Overt Aggression Scale • BPRS, total and subscale scores	
Migraine Prophylaxis					
Linde et al[133] 2013 Cochrane Review (10 prospective, controlled trials)	N=848	Prevention of episodic migraine in adults	Valproic acid derivatives	<u>Headache Reduction (2 trials)</u> • Mean difference (MD) -4.31 (95% CI -0.83 to -0.30) <u>Responders</u> • Divalproex > Placebo (4 trials) ○ RR 2.18 (1.28-3.72; NNT=4; 95% CI 2-11) • Valproate Sodium > Placebo (1 trial) ○ RR 2.83 (95% CI 1.27-6.31; NNT=3; 95% CI 2-9) <u>Post-Treatment Mean Headache Frequency (2 trials)</u> • Topiramate > Valproate ○ Mean difference -0.90 (95% CI -1.58 to -0.22)	Valproate was well tolerated <u>Adverse Events NNH (95% CI)</u> • Dizziness/vertigo ○ 14 (8-100) • Nausea ○ 7 (4-25) • Tremor ○ 14 (8-14) • NNH 95% CI included zero for ○ Asthenia/fatigue ○ Weight gain <u>Clinically Important Adverse Events</u> • Number needed to harm ○ 7-14

KEY: HR=harms ratio; CI=confidence interval; RCT=randomized, controlled trial; MC=multicenter; DB=double-blind; IV=intravenous; HR=heart rate; BP=blood pressure; RR=respiratory rate; OL=open label; PRO=prospective; YMRS=Young Mania Rating Scale; CDRS= Children's Depression Rating Scale; ;BPRS=Brief

Psychiatric Rating Scale; PC=placebo controlled; PG=parallel group; SB=single-blinded; CGI-I=Clinical Global Impressions-Improvement; CGI-BP=Clinical Global Impressions –Bipolar Version; MRS=Mani Rating Scal

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